POWER OF ATTORNEY

#10

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| **In re:** | U.S. Patent No. 6,589,508 | **Inventors:** | Aberg *et al.* |
| **Issued:** | July 8, 2003 | **Atty Dckt No.:** | 4821-604-999<br>(CAM 208423-600008) |
| **Assignee:** | Sepracor Inc. | | |
| **For:** | Methods and Compositions for Treating Pulmonary Disorders Using Optically Pure (R,R) Formoterol | | |

## POWER OF ATTORNEY

Mail Stop Post Issue
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Sepracor Inc. (assignee) hereby appoints:

☒ Practitioners at Customer Number 20583

as his/her/its/their attorney(s) or agent(s) to prosecute the Application for Extension of Patent Term Under 35 U.S.C. § 156 filed herewith in connection with the above-identified patent.

Please direct all correspondence in connection with the Application for Extension of Patent Term Under 35 U.S.C. § 156 filed in connection with the above-identified patent to:

☒ The above mentioned Customer Number.

☒ Firm or Individual Name:

Address: Jones Day, 222 East 41st Street, New York, New York 10017

Telephone: (212) 326-3939

Sepracor Inc. is the:

☐ Applicant/Inventor
☒ Assignee of record of the entire interest. See 37 CFR 3.71.
*(Statement under 37 CFR 3.73(b) is applicable)*

**Statement Under 37 C.F.R. 3.73(b)**

Sepracor Inc. states that it is:

☒ the Assignee of the entire right, title, and interest; or
☐ an assignee of less than the entire right, title and interest.
The extent (by, percentage) of its ownership interest is %

1. The above-identified application is a continuation of U.S. Application No. 09/535,200, filed March 27, 2000, now U.S. Patent No. 6,299,863, which is a continuation of U.S. Application No. 09/136,109, filed August 18, 1998, now U.S. Patent No. 6,068,833, which is a continuation of U.S. Application No. 08/613,382, filed March 7, 1996, now U.S. Patent No. 5,795,564. An assignment in connection with U.S. Application No. 08/613,382 from Gunnar Aberg and John Morley to Sepracor Inc. was recorded in the United States Patent and Trademark Office on July 5, 1996 at Reel 008018 / Frame 0813.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

**ASSIGNEE: Sepracor Inc.**

Date: 29th November, 2006 Signature: Robt T. Barker

Typed Name: Robert T. Barker

Position/Title: Assistant Secretary

Note: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required.

ROBERT T. BARKER
ASSISTANT SECRETARY
SEPRACOR INC

09/927,008 12-04-06

DFE


**Express Mail: EB 083401548 US**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**In re:** U.S. Patent No. 6,589,508 **Attorney Docket No.:** 4821-604-999 (CAM: 208423-600008)

**Issued:** July 8, 2003

**Inventors:** Aberg *et al.*

**Assignee:** Sepracor Inc.

**For:** Methods and Compositions for Treating Pulmonary Disorders Using Optically Pure (R,R) Formoterol

**MAIL STOP PATENT EXTENSION**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**FEE TRANSMITTAL LETTER**
**FOR AN APPLICATION FOR EXTENSION UNDER 35 U.S.C. § 156**

Sir:

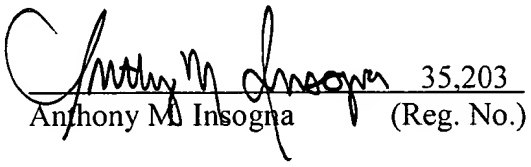
Transmitted herewith is an Application for Extension of Patent Term Under 35 U.S.C. § 156 for U.S. Patent No. 6,589,508, accompanied by two additional copies. The undersigned attorney for Applicant hereby states that these copies are certified to be duplicates of the original. Each copy contains the following exhibits:

| | |
|---|---|
| Exhibit A | U.S. Patent No. 6,589,508 |
| Exhibit B | Assignment Recordation & Assignment |
| Exhibit C | Approved Product Label |
| Exhibit D | FDA Approval Letter |
| Exhibit E | Terminal Disclaimer |
| Exhibit F | Maintenance Fee Payment Record |
| Exhibit G | Compendium of Significant Regulatory Activities in Connection with BROVANA™ IND and NDA |

Please charge the required fee estimated to be $1,120.00 to Jones Day Deposit Account No. 50-3013. The Director is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: December 1, 2006



35,203
Anthony M. Insogna (Reg. No.)

**JONES DAY**
222 East 41st Street
New York, NY 10017
(212) 326-3939

**Express Mail: EB 083401548 US**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**In re:** U.S. Patent No. 6,589,508 **Attorney Docket No.:** 4821-604-999 (CAM: 208423-600008)

**Issued:** July 8, 2003

**Inventors:** Aberg *et al.*

**Assignee:** Sepracor Inc.

**For:** Methods and Compositions for Treating Pulmonary Disorders Using Optically Pure (R,R) Formoterol

**MAIL STOP PATENT EXTENSION**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156**

Sir:

In accordance with 35 U.S.C. § 156 and 37 C.F.R. § 1.740, Sepracor Inc., through the undersigned, represents that it is the owner of record of United States Patent No. 6,589,508 ("the '508 patent"), attached hereto as Exhibit A, and hereby requests an extension of the patent term thereof. A copy of the assignment and assignment recordation from the United States Patent and Trademark Office ("USPTO") for U.S. Patent No. 5,795,564, which is the great grandparent of the '508 patent, and which was recorded at Reel 8147, frame 0954, confirming that all right, title, and interest resides in Sepracor Inc., is attached hereto as Exhibit B.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740. The sections of this application are numbered in a manner corresponding with the numbering of subparagraphs (1) to (15) of 37 C.F.R. § 1.740(a) and follow the format set forth therein.

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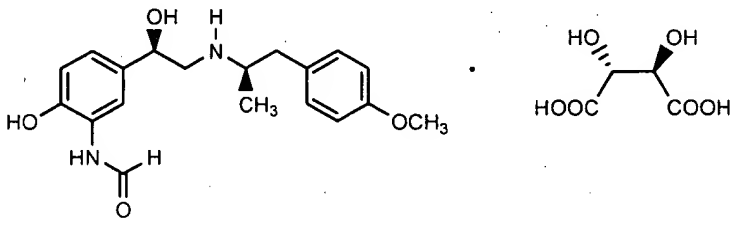
01 FC:1457 1120.00 DA

12/05/2006 SDENBOB1 00000040 503013 6589508
01 FC:1253 1020.00 CR

***(1) "A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics."***

The approved product is BROVANA™, the active ingredient of which is arformoterol tartrate. A chemical name of arformoterol tartrate is formamide, N-[2-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]- (2R,3R)-2,3-dihydroxybutanedioate (1:1 salt), and the structure is shown as below:




Synonyms for arformoterol include "the (R,R)-enantiomer of formoterol," "(R,R)-isomer of formoterol," or "(R,R)-formoterol." The molecular weight of arformoterol tartrate is 494.5 g/mol, and its empirical formula is $C_{19}H_{24}N_2O_4 \cdot C_4H_6O_6$. (*See* Product Label at Exhibit C, page 1, lines 24-25).

As currently approved, BROVANA™ is indicated for the long-term maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease ("COPD"), including chronic bronchitis and emphysema. (*See* Product Label, page 8, lines 283-286). Currently, the approved product is available in the form of an inhalation solution, 15 mcg/2 mL (arformoterol; equivalent to 22 mcg of arformoterol tartrate), for oral inhalation. (*See* Product Label at Exhibit C, page 19, lines 631-633).

***(2) "A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred."***

BROVANA™ was subject to regulatory review for an investigational new drug application ("IND") and a new drug application ("NDA") under section 505 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355 ("FFDCA"). Section 505(b) of the FFDCA, 21 U.S.C. §355(b), authorizes the filing of an NDA for a new drug. The Food and Drug Administration ("FDA") subsequently approved the BROVANA™ NDA (21-912) under the authority granted by section 505(c) of the FFDCA, 21 U.S.C. § 355(c).

***(3) "An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred."***

BROVANA™ received permission for commercial marketing or use by the FDA pursuant to section 505(b) of the FFDCA, 21 U.S.C. § 355(b), on October 6, 2006. Copies of the Product Label and FDA Approval Letter are attached as Exhibits C and D, respectively.

***(4) "In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum- Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved."***

The active ingredient in BROVANA™ is arformoterol tartrate. Arformoterol tartrate has not been previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act or the Virus-Serum-Toxin Act.

***(5) "A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the last day on which the application could be submitted."***

This application is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. § 1.720(f), the last day for said submission being December 4, 2006.

***(6) "A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration."***

The complete identification of the patent for which extension is sought is as follows:

| | |
|---|---|
| Inventors: | Gunnar Aberg and John Morley |
| Patent No.: | 6,589,508 |
| Issue Date: | July 8, 2003 |
| Expiration Date: | April 3, 2012 |

***(7) "A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings."***

A copy of U.S. Patent No. 6,589,508 ("the '508 patent"), for which this extension is sought, is attached hereto as Exhibit A.

***(8 ) "A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent."***

A copy of the terminal disclaimer filed December 5, 2002, which disclaims the terminal part of the '508 patent extending beyond the expiration of U.S. Patent No. 5,795,564, is attached hereto as Exhibit E.

No reexamination certificate for the '508 patent was issued.

A copy of the 4th year maintenance fee receipt is attached hereto as Exhibit F; thus, no maintenance fee is currently due. The 8th year maintenance fee is not due until 2010.

***(9) "A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on: (i) The approved product, if the listed claims include any claim to the approved product;***
***(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and***
***(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product."***

The '508 patent claims, *inter alia*, a method of using the active ingredient of the approved product BROVANA™. More specifically, at least independent claims 7 and 13 of the '508 patent, and at least dependent claims 8-9 and 14-15, claim methods of using the active ingredient of the approved product. Exemplary claims are set forth below:

Claim 7

> A method of treating or preventing bronchospasm in a human, the method comprising administering to the human a therapeutically effective amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight of (S,S)-formoterol, or a pharmaceutically acceptable salt thereof.

Claim 13

> A method of eliciting bronchodilation effect in a human, the method comprising administering to the human a therapeutically effective amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof.

The Product Label for the approved product states that BROVANA™ is indicated for the long term maintenance treatment of bronchoconstriction. (*See* Product Label at Exhibit C, page 9, lines 283-285). The Product Label also indicates that, in clinical trials, administration of BROVANA™ resulted in significantly greater post-dose bronchodilation compared to placebo. (*See* Product Label at Exhibit C, page 7, lines 258-261). Thus, claims 7 and 13 claim methods of using the approved product.

The Product Label for the approved product states that the recommended dose of BROVANA™ for COPD patients is 15 microgram administered twice daily by nebulization. (*See* Product Label, page 18, lines 608-610). Thus, at least dependent claims 8-9 and 14-15 also claim methods of using the approved product.

***(10) "A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:***

***(i) For a patent claiming a human drug, antibiotic, or human biological product:***

***(A) The effective date of the investigational new drug (IND) application and the IND number;***

***(B) The date on which a new drug application (NDA) or a Produce License Application (PLA) was initially submitted and the NDA or PLA number; and***

***(C) The date on which the NDA was approved or the Product License issued."***

The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period for BROVANA™ are as follows:

(a) Investigational new drug ("IND") application number 55,302 was received by the FDA on February 24, 1998 and became effective on March 26, 1998, which is 30 days after the receipt of the IND by the FDA.

(b) The new drug application ("NDA") was submitted on December 8, 2005, and was later assigned NDA number 21-912.

(c) NDA number 21-912 was approved by the FDA on October 6, 2006 (Exhibit D).

*(11) "A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities."*

A chronology of selected regulatory activities is attached hereto as Exhibit G to briefly describe certain activities undertaken with respect to the approval of BROVANA™ during the applicable regulatory review period and the dates applicable to such activities.

*(12) "A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined."*

Applicant is of the opinion that the '508 patent is eligible for an extension and estimates the extension to be **745 days**, the calculation of which is described below.

A. Eligibility:

(a) Pursuant to 35 U.S.C. § 156(a), the '508 patent claims a method of using the active ingredient;

(b) Pursuant to 35 U.S.C. § 156(a)(1), the term of the '508 patent has not expired before submission of this application for extension;

(c) Pursuant to 35 U.S.C. § 156(a)(2), the term of the '508 patent has never been extended;

(d) Pursuant to 35 U.S.C. § 156(a)(3), the application for extension is submitted by the owner of record of the '508 patent;

(e) Pursuant to 35 U.S.C. § 156(a)(4), the approved product, BROVANA™, has been subject to a regulatory review period before its commercial marketing or use;

(f) Pursuant to 35 U.S.C. § 156(a)(5), the permission for the commercial marketing or use of BROVANA™ after the regulatory review period is the first permitted commercial marketing or use of this product;

(g) Pursuant to 35 U.S.C. § 156(c)(4), no other patent has been extended for the same regulatory review period for the approved product BROVANA™.

B. Regulatory Review Period:

(a) Pursuant to 37 C.F.R. § 1.775(c)(1), the period from March 26, 1998 (the date IND application number 55,302 became effective) to December 8, 2005 (the date the NDA was initially submitted) is 2,815 days. Accordingly, Applicant calculates the "Testing Phase" as 2,815 days.

(b) Pursuant to 37 C.F.R. § 1.775(c)(2), the period from December 8, 2005 (the date the NDA was initially submitted) to October 6, 2006 (the date of NDA approval) is 303 days. Accordingly, Applicant calculates the "Approval Phase" as 303 days.

C. Extended Patent Term:

(a) The number of days in the regulatory review period which were on and before July 8, 2003, the date on which the '508 patent issued, is 1,931 days. Accordingly, 1,931 days are subtracted from the regulatory review pursuant to 37 C.F.R. § 1.775(d)(1)(i). Thus, Applicant calculates the "Adjusted Testing Phase" to be 884 days.

(b) As demonstrated in Exhibit G, the Applicant acted with due diligence during the regulatory review period. Accordingly, zero (0) days are subtracted from the regulatory review period pursuant to 37 C.F.R. § 1.775(d)(1)(ii).

(c) One half of the number of days remaining in the Testing Phase after the above reductions is 442 days. Accordingly, 442 days are subtracted from the regulatory review period pursuant to 37 C.F.R. § 1.775(d)(1)(iii).

(d) The period remaining in the term of the patent (set to expire April 3, 2012) measured from the date of approval of BROVANA™ (October 6, 2006) (2,007 days) when added to the period of extension (745 days) is 2,752 days, which is less than fourteen (14) years. Accordingly, the fourteen (14) year limitation set forth in 37 C.F.R. § 1.775(d)(2)-(4) does not operate to further reduce the regulatory review period.

(e) The period of extension (745 days) is less than five (5) years. Accordingly, the five (5) year limitation set forth in 37 C.F.R. § 1.775(d)(5)(i)(ii) does not operate to further reduce the regulatory review period.

Period of Extension = ½ (Adjusted Testing Phase) + Approval Phase
= ½ (884) + 303
= **745 days**

***(13) "A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to any determination of entitlement to the extension sought."***

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought pursuant to 37 C.F.R. § 1.765.

***(14) "The prescribed fee for receiving and acting upon the application for extension."***

The prescribed fee for receiving and acting upon this application is believed to be $1,120.00 pursuant to 37 C.F.R. § 1.20(j)(1). The Director is authorized to charge this fee and any additional required fees, or credit any overpayment, to Jones Day Deposit Account No. 50-3013.

***(15) "The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed."***

Please direct all inquiries and correspondence relating to this application to:

Anthony M. Insogna, Esq.
**JONES DAY**
222 East 41st Street
New York, New York 10017
(212) 326-3939

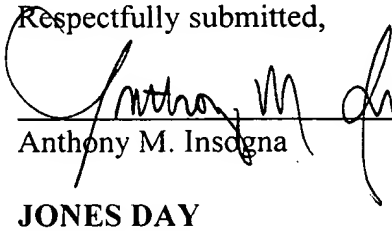
A power of attorney is also enclosed so that the record will reflect correspondence should be addressed to Customer No. 20583.

*(16) "The application under this section must be accompanied by two additional copies of such application (for a total of three copies)."*

This Application is accompanied by two additional copies of such application for a total of three copies as required by 37 C.F.R. § 1.740(b). The undersigned attorney for Applicants hereby states that these copies are accurate and true duplicates of the original.

Respectfully submitted,

Date: December 1, 2006



35,203
Anthony M. Insogna (Reg. No.)

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New York, NY 10017
(212) 326-3939

US006589508B1

(12) **United States Patent**
**Aberg et al.**

(10) **Patent No.: US 6,589,508 B1**
(45) **Date of Patent: *Jul. 8, 2003**

(54) **METHODS AND COMPOSITIONS FOR TREATING PULMONARY DISORDERS USING OPTICALLY PURE (R,R) FORMOTEROL**

(75) Inventors: **Gunnar Aberg**, Westborough, MA (US); **John Morley**, Richmond-upon-Thames (GB)

(73) Assignee: **Sepracor Inc.**, Marlborough, MA (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/927,008**

(22) Filed: **Aug. 9, 2001**

**Related U.S. Application Data**

(63) Continuation of application No. 09/535,200, filed on Mar. 27, 2000, which is a continuation of application No. 09/136,109, filed on Aug. 18, 1998, now Pat. No. 6,068,833, which is a continuation of application No. 08/613,382, filed on Mar. 7, 1996, now Pat. No. 5,795,564, which is a continuation-in-part of application No. 08/373,515, filed on Jan. 12, 1995, now abandoned, which is a continuation-in-part of application No. 08/222,319, filed on Apr. 4, 1994, now abandoned, which is a continuation of application No. 07/927,458, filed on Aug. 10, 1992, now abandoned, said application No. 09/136,109, filed on Aug. 18, 1998, is a continuation-in-part of application No. 08/382,744, filed on Feb. 2, 1995, now abandoned, which is a continuation of application No. 08/223,798, filed on Apr. 6, 1994, now abandoned, which is a continuation of application No. 07/862,907, filed on Apr. 3, 1992, now abandoned.

(30) **Foreign Application Priority Data**

Apr. 5, 1991 (GB) ..... 9107196

(51) **Int. Cl.**[7] ..... **A61K 9/00**; A61K 9/12; A61K 9/20; A61K 9/70

(52) **U.S. Cl.** ..... **424/45**; 424/46; 424/489; 424/400; 424/443; 424/451; 424/464; 514/826

(58) **Field of Search** ..... 424/45, 46, 400, 424/489, 443, 451, 464; 514/826

(56) **References Cited**

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| 5,795,564 A | * | 8/1998 | Aberg et al. | 424/45 |
| 6,068,833 A | * | 5/2000 | Aberg et al. | 424/45 |

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| | | |
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| GB | 2255503 | 11/1992 |
| WO | WO92/05147 | 4/1992 |

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Hett et al, Enantio- and Diastereoselective Synthesis of all Four Steroisomers of Formoterol, Tet. Lett. 38, 1125–1128 (1997).*

"Comparison of the Action of BD 40 A and some Other β–Adrenoceptor Stimulants of the Isolated Trachea and Atria of the Guinea Pig" H. Ida *Arzneim.–Forsch.* 26,839–842 (1976).

"Cardiorespiratory Activities of 3–Formylamino–4–hydroxy α–(N–1–methyl–2–methoxyphenethylaminomethyl)–benzylalcohol–bemifumarate (BD 40 ) and some other β–Adrenoceptor Stimulants in Conscious Guinea Pigs" H. Ida *Arzneim.–Forsch. 26*, 1337–1340 (1976).

"New β–Adrenoreceptor Stimulants. Studies on 3–Acylamino–4–hydroxy–α–(N–substituted aminomethyl–)benzyl Alcohols" Murase et al. *Chem. Pharm. Bull. 25*(6) 1368–1377 (1977).

"Steric Aspects of Agonism and Antagonism at β–Adrenoceptors: Synthesis of and Pharmacological Experiments With the Enantiomers of Formoterol and Their Diasteromers" Trofast et al. *Chirality* 3443–450 (1991).

"A Three–Month Comparison of Twice Daily Inhaled Formoterol Versus Four Times Daily Inhaled Albuterol in the Management of Stable Asthma [1–3]" Kesten et al. *Am. Rev. Respir. Dis. 144* 622–625 (1991).

"Absolute Configurations of Four Isomers of 3–Formamido–4–hydroxy– . . . " Murase et al. *Chem. Pharm. Bull. 26*, 1123–29 (1978).

"β–Adrenoceptor Ligands: Characterization and Quantification of Drug Effects" Lemoine *Quant. Struct.–Act. Relat. 11*, 211–218 (1992).

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"Racemates Versus Enantiomers in Drug Development: Dogmatism . . . " Testa et al. *Chirality 2*, 129–133 (1990).

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Testa et al., "Racemates Versus Enatiomers in Drug Development: Dogmatism or Pragmatism?" *Chirality*, 2:129–133 (1990).

* cited by examiner

*Primary Examiner*—Michael G. Hartley
*Assistant Examiner*—M. Haghighatian
(74) *Attorney, Agent, or Firm*—Heslin Rothenberg Farley & Mesiti, P.C.; Candice J. Clement, Esq.

(57) **ABSTRACT**

A method and composition are disclosed utilizing the pure (R,R) isomer of formoterol, which is a potent bronchodilator with reduced adverse effects, having a low incidence of the development of tolerance and having increased duration of action.

**18 Claims, No Drawings**

# METHODS AND COMPOSITIONS FOR TREATING PULMONARY DISORDERS USING OPTICALLY PURE (R,R) FORMOTEROL

## CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Ser. No. 09/535,200, filed Mar. 27, 2000 as a continuation of U.S. Ser. No. 09/136,109 (now U.S. Pat. 6,068,833), filed Aug. 18, 1998 as a continuation of U.S. Ser. No. 08/613,382 (now U.S. Pat. No. 5,795,564), filed Mar. 7, 1996 as a continuation-in-part of U.S. Ser. No. 08/373,515 (now abandoned), filed Jan. 12, 1995 as a continuation-in-part of U.S. Ser. No. 08/222,319 (now abandoned), filed Apr. 4, 1994 as a continuation of U.S. Ser. No. 07/927,458 (now abandoned), filed Aug. 10, 1992. U.S. Ser. No. 09/136,109 also claims priority as a continuation-in-part of U.S. Ser. No. 08/382,744 (now abandoned), filed Feb. 2, 1995 as a continuation of U.S. Ser. No. 08/223,798 (now abandoned), filed Apr. 6, 1994 as a continuation of U.S. Ser. No. 07/862,907 (now abandoned), filed Apr. 3, 1992 claiming priority of Great Britain application 9107196.9, filed Apr. 5, 1991. The entire disclosures of each of the prior applications are incorporated herein by reference.

## BACKGROUND OF THE INVENTION

This invention relates to novel compositions of matter containing optically pure (R,R) formoterol. These compositions possess potent, long-lasting bronchodilating activity as β-adrenergic agonists while avoiding or reducing adverse effects including but not limited to muscle tremor and tachycardia as well as avoiding or reducing the development of tolerance or hypersensitivity on repeated administration. The compositions also provide an improved duration of action. This invention also relates to methods of treating asthma, bronchitis, emphysema, bronchospasms, and other ailments in patients with obstructive airway or allergic disorders while avoiding adverse effects, development of tolerance or hypersensitivity on repeated administration or a limited pattern of bronchial distribution when administered by inhalation.

The active compound of these compositions and methods is an optical isomer of formoterol, which is described by Ida in Arzneim, Forsch. 26, 839–842 and 1337–1340 (1976) and in U.S. Pat. No. 3,994,974. Chemically, the active compound is N-hydroxy-5-(1-hydroxy-2-[(2-(4-methoxyphenyl) methylethyl]amino]ethyl]phenylformamide, which exists as two enantiomeric pairs of diastereomers. Of these, the R,R diastereomer is the most active and, when substantially optically pure, will be hereinafter referred to as (R,R) formoterol. Formoterol is available commercially only as a racemic diastereomer, (R,R) plus (S,S) in a 1:1 ratio, and the generic name formoterol refers to this enantiomeric mixture. The racemic mixture of (±) formoterol that is commercially available for administration is a dihydrate of the fumarate salt.

When two chiral centers occur in the same molecule each of them can exist in two possible configurations. This gives rise to four combinations: (R,R), (S,S), (R,S) and (S,R). (R,R) and (S,S) are mirror images of each other and are therefore enantiomers which share chemical properties and melting points just like any other enantiomeric pair. (R,S) and (S,R) are similarly an enantiomeric pair. The mirror images of (R,R) and (S,S) are not, however, superimposable on (R,S) and (S,R). This relationship is called



diastereomeric, and (R,R) is a diastereomer of (R,S). Formoterol, having two chiral centers, falls into this category.

Adrenergic or sympathomimetic drugs are so called because they are understood to exert their effect through their action on the body's adrenergic receptors of which there are three functionally divided types, the α, $\beta_1$ and $\beta_2$ receptors. On the basis of their interaction with these three receptor types, the adrenergic or sympathomimetic drugs are in turn classifiable into three groups:

1.1 Non-selective sympathomimetic drugs;

1.2 Non-selective β sympathomimetic drugs; and

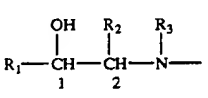
1.3 Selective $\beta_2$sympathomimetic bronchodilator drugs.

Drugs of group 1.1 exert both α and β sympathomimetic effects. They include the drug substances adrenaline and ephedrine. Both adrenaline and ephedrine are known clinically as bronchodilators. Though adrenaline, despite side effect induced via its α-sympathomimetic properties, is still used by some practitioners for the treatment of acute asthma, both adrenaline and ephedrine have been largely superseded in asthma therapy.

The drugs of group 1.2 have both $\beta_1$ and $\beta_3$ sympathomimetic activity but no, or only limited, α-sympathomimetic activity. Of the group 1.2 drugs, isoprenaline is the best known representative. Isoprenaline differs from the drugs of group 1.3 in its faster onset but shorter duration of action and its cardiac stimulating effects which result largely from its $\beta_1$ activity. Though isoprenaline has previously been extensively used as bronchodilator therapy in asthma, its use has today become clinically restricted. Thus, in the UK, a rise in the rate of asthma death in the 1960's believed to have been specifically associated with isoprenaline usage has resulted in discontinuation of its clinical application.

The selective $\beta_2$ sympathomimetic bronchodilator drugs of group 1.3 (herein referred to for convenience collectively as "Group 1.3 drugs") act, as their name implies, selectively on the $\beta_2$ adrenergic receptors. The Group 1.3 drugs include for example, the drug substances terbutaline, albuterol, fenoterol, isoetharine, metaproterenol and, more recently, the so-called "long acting selective $\beta_2$ sympathomimetic bronchodilator drug substances" formoterol, bambuterol and salmeterol. All of the above recited Group 1.3 drugs are commercially available and clinically used, generally in pharmaceutically acceptable salt form, e.g. as the sulphate, hydrobromide, hydrochloride, fumarate or methanesulfonate or, where appropriate, one or other of the hydrate forms thereof.

Group 1.3 drugs characteristically contain as part of their structure an ethanolamine or 2-amino-ethanol moiety of formula I




(I)

in which $R_1$ is an aromatic group. Commonly $R_1$ is 3,4-or 3,5-dihydroxyphenyl or 4-hydroxy-3-hydroxymethylphenyl. $R_1$ may also be 3-formylamino-4-hydroxyphenyl, as in the case of formoterol. $R_2$ and $R_3$ in formula I are commonly H. Since the formula I moiety comprises at least 1 asymmetric carbon atom (Cl in formula I), all of the Group 1.3 drugs exist in optically active isomeric form, with the chiral carbon atom having the (R) or (S) configuration [as designated using the Cahn-Ingold-

Prelog system (Angew. Chem. Intern. Ed. 5, 385–415 (1966)]. When the Cl carbon atom is the sole asymmetric carbon atom present, Group 1.3 drugs thus exist as individual (R) or (S) enantiomers or in racemic [(RS)] form, i.e. as a 50:50 mixture of the (R) and (S) enantiomers.

Individual Group 1.3 drugs in which $R_2$ in the formula I moiety is other than H, or in which the remainder of the molecule includes an asymmetric carbon atom (e.g. formoterol) exist in a variety of isomeric forms, i.e. in individual (R,R), (S,S) (R,S) and (S,R) isomeric form, as racemic [(RS,RS) and (RS,SR)] mixtures comprising the (R,R) plus (S,S) and (R,S) plus (S,R) enantiomeric pairs, as well as in the form of diastereomeric mixtures comprising all four isomeric forms.

The Group 1.3 drugs can be administered orally, parenterally or (most commonly) by inhalation, e.g. using nebulizers or metered aerosol devices or as inhaled powders. Inhalation of Group 1.3 drugs presently represents the mainstay of bronchodilator therapy for the treatment of asthma of all grades of severity. The duration of bronchodilatation induced by the majority of Group 1.3 drugs is relatively short and they are employed to relieve asthma attack as and when it occurs. As indicated above, the more recently introduced Group 1.3 drugs, such as formoterol, are characterized by their longer duration of action and hence apparent reduced frequency of dosaging required.

Although the Group 1.3 drugs are effective and generally seem to be well tolerated, their safety, especially at high dosages, has been questioned over many years and numerous reports have appeared on the adverse effects of Group 1.3 drug therapy (see e.g. Paterson et al: *American Review of Respiratory Disease* 120, 844–1187 (1979) especially at page 1165 et seq.). More recently, from New Zealand, where a continuing increase in asthma death has been recorded, two case control studies reported in *The Lancet* have linked increase in asthma mortality to use of the Group 1.3 drug, fenoterol—see in particular: Editorial "$\beta_2$ agonists in asthma: relief, prevention, morbidity", *Lancet* 336, 1411–1412 (1990). A subsequently reported Canadian study finds that the use of inhaled Group 1.3 drugs, principally fenoterol and albuterol, is associated with "an increased risk of the combined outcome of fatal and near-fatal asthma, as well as of death from asthma alone"—see Spitzer et al., *New England J. Med.* 326 (8), 501–506 (1992) and the Editorial to the same issue at page 560.

Various possible explanations for observed episodes of increased airway obstruction, arterial hypoxaemia or "anomalous" or "paradoxical" bronchospasm, as well as increased morbidity associated with Group 1.3 drug usage, in particular long term/high dose usage, have been proposed. These have included, for example, reactive myogenic tone, increased inflammatory burden, adrenoceptor tachyphylaxis and induction of airway hyperreactivity, as well as the involvement of spasmogenic drug metabolic products or long term influence of aerosol spray propellants—see e.g. Paterson et al. loc. cit. and Morley et al., *Eur. Respir. J.* 3, 1–5 (1990).

There is mounting concern within the medical profession as to the potential dangers of Group 1.3 drug usage in asthma therapy. To quote the Lancet editorial already referred to:

> "These studies raise serious question about the use of β agonists [i.e. Group 1.3 drugs]. The findings of Sears et al. could be interpreted as supporting the current trend towards earlier use of corticosteroids and other preventers of inflammation [for asthma therapy] rather than perseverance with an escalating bronchodilator regimen. The findings of the Nottingham and Dunedin groups also indicate that there is some way to go before long acting β2 agonist preparations such as salmeterol and formoterol can be unreservedly recommended for routine use in the management of asthma. There seem to be clear advantages of compliance and possibly of anti-inflammatory activity associated with such agents, but the potential for adverse effects cannot be ignored. Clinicians researchers and pharmaceutical companies must now attempt to redefine the use of β2 agonists in asthma." [Emphasis added.]

Equally there has been evident inability or reluctance to conceive of any problem in relation to Group 1.3 drug therapy as being inherent in Group 1.3 drugs themselves or as hitherto employed—cf. the following, taken from the editorial in the *New England Journal of Medicine* also previously referred to:

> "Although . . . too much reliance is placed on beta-agonists (Group 1.3 drugs], it is difficult to believe that the problem is related directly to the more regular use of inhaled beta-agonists."

While the suitability, in particular of high-dose or long-term, Group 1.3 drug therapy has long been a subject of debate and, more recently, acute question, the practice of administering drugs of this group as racemic mixtures has continued. This practice has been accepted by drug registration authorities world-wide and even the most recently introduced of the Group 1.3 drugs have been developed for clinical use as racemic mixtures. This practice is based upon the assumption or understanding that the non-bronchodilator component of the racemic mixture, i.e. the bronchodilatorily less or inactive enantiomer (distomer) is devoid of any relevant drug effect and can thus be administered together with the bronchodilatorily active isomer (eutomer) essentially as inactive ballast and without risk to the patient. The teaching of the present invention thus stands in stark opposition to long, widely established and continuing practice. The present invention thus runs contrary to the wisdom of the art. In that the Group 1.3 drugs clearly offer very considerable potential benefit for bronchodilator usage in asthma, the need to find a means of avoiding, ameliorating or restricting disadvantages inherent in their use is urgent and crucial. By meeting this need, the present invention may be anticipated to bring immeasurable benefit both to the medical profession and the world asthma population.

Formoterol, which is the subject of the present invention, is available only as a racemic mixture of the (R,R) and (S,S) diastereomers. Trofast et al. [*Chirality* 3, 443–450 (1991)] have described the preparation of each of the substantially pure isomers. They concluded that "Since the (S,S)-enantiomer is practically inactive there is from this point of view no reason for its removal from the racemate in pharmaceutical preparations . . . ".

Formoterol's primary use is as a long-acting bronchodilator for the relief of reversible bronchospasm in patients with obstructive airway disease such as asthma, bronchitis and emphysema.

Asthma, bronchitis and emphysema are known as Chronic Obstructive Pulmonary Diseases (COPD). COPD is characterized as generalized airways obstruction, particularly of small airways, associated with varying degrees of symptoms of chronic bronchitis, asthma, and emphysema. The term COPD was introduced because these conditions often coexist, and it may be difficult in an individual case to decide which is the major condition producing the obstruction. Airways obstruction is defined as an increased resistance to airflow during forced expiration. It may result from narrowing or obliteration of airways secondary to intrinsic airways

disease, from excessive collapse of airways during a forced expiration secondary to pulmonary emphysema, from bronchospasm as in asthma, or may be due to a combination of these factors. Although obstruction of large airways may occur in all these disorders, particularly in asthma, patients with severe COPD characteristically have major abnormalities in their small airways, namely those less than 2 mm internal diameter, and much of their airways obstruction is situated in this zone. The airways obstruction is irreversible except for that which can be ascribed to asthma.

Asthma is a reversible obstructive lung disorder characterized by increased responsiveness of the airways. Asthma can occur secondarily to a variety of stimuli. The underlying mechanisms are unknown, but inherited or acquired imbalance of adrenergic and cholinergic control of airways diameter has been implicated. Persons manifesting such imbalance have hyperactive bronchi and, even without symptoms, bronchoconstriction may be present. Overt asthma attacks may occur when such persons-are subjected to various stresses, such as viral respiratory infection, exercise, emotional upset, nonspecific factors (e.g., changes in barometric pressure or temperature), inhalation of cold air or irritants (e.g., gasoline fumes, fresh paint and noxious odors, or cigarette smoke), exposure to specific allergens, and ingestion of aspirin or sulfites in sensitive individuals. Psychologic factors may aggravate an asthmatic attack but are not assigned a primary etiologic role.

Persons whose asthma is precipitated by allergens (most commonly airborne pollens and molds, house dust, animal danders) and whose symptoms are IgE-mediated are said to have allergic or "extrinsic" asthma. They account for about 10 to 20% of adult asthmatics; in another 30 to 50%, symptomatic episodes seem to be triggered by nonallergenic factors (e.g., infection, irritants, emotional factors), and these patients are said to have nonallergic or "intrinsic" asthma. In many persons, both allergenic and nonallergenic factors are significant. Allergy is said to be a more important factor in children than in adults, but the evidence is inconclusive.

Chronic bronchitis (unqualified) is a condition associated with prolonged exposure to nonspecified bronchial irritants and accompanied by mucus hypersecretion and certain structural changes in the bronchi. Usually associated with cigarette smoking, it is characterized clinically by chronic productive cough. The term chronic obstructive bronchitis is used when chronic bronchitis is associated with extensive abnormalities of the small airways leading to clinically significant airways obstruction. (Pulmonary emphysema is enlargement of the air spaces distal to terminal nonrespiratory bronchioles, accompanied by destructive changes of the alveolar walls.) The term chronic obstructive emphysema is used when airways obstruction is also present and where it is clear that the major features of the disease can be explained by emphysematous changes in the lungs.

Many of the $\beta_2$ agonists cause somewhat similar adverse effects. These adverse effects include but are not limited to the central nervous system symptoms such as hand tremors, muscle tremors, nervousness, dizziness, headache and drowsiness; respiratory side effects such as dyspnea, wheezing, drying or irritation of the oropharynx, coughing, chest pain and chest discomfort; cardiovascular effects such as palpitations, increased heart rate, and tachycardia. According to Trofast et al. (op. cit.) (R,R) formoterol is primarily a chronotropic agent in vitro with inotropic effects showing up at higher concentrations. The chronotropic effects are reported at concentrations that are higher than those at which relaxation of tracheal muscle (bronchodilation) is seen. β-Agonists (e.g. dobutamine) are known in general to exhibit inotropic activity. In addition, racemic $\beta_2$-agonists can cause angina, vertigo, central stimulation and insomnia, airway hyperreactivity (hypersensitivity), nausea, diarrhea, dry mouth and vomiting. As with other pharmaceuticals $\beta_2$-agonists sometimes cause systemic adverse effects such as weakness, fatigue, flushed feeling, sweating, unusual taste, hoarseness, muscle cramps and backaches.

Furthermore, patients have a tendency to develop a tolerance to the bronchodilating effect of the racemic mixture of formoterol. This is related to desensitization, which is one of the most clinically significant phenomena involving the beta-adrenergic receptor. It has been observed that patients in prolonged beta-agonist therapy have a tendency to increase the dosage of drug they use. This occurs because after prolonged administration, the beta-receptor appears to become desensitized to the agonist, thus requiring larger doses of the compound to effect an equivalent physiological response.

The problem of desensitization is especially significant in the treatment of diseases involving bronchospasms, such as asthma. The treatment of asthma usually involves the self-administration either orally or by aerosol, of beta-adrenergic agonists such as the racemic (R,R) (S,S) mixture of formoterol. These agonists mediate bronchodilation and promote easier breathing. Asthmatic patients utilizing β-agonists for a prolonged time gradually increase the self-administered dose in order to get a sufficient amount of bronchodilation and relief in breathing. As a result of this increased dosage, the agonist concentration builds to a sufficient level so as to enter the peripheral circulation where it acts on the beta receptors of the heart and vasculature to cause cardiovascular stress and other adverse effects.

Moreover, when administering the racemic mixture of formoterol by inhalation, because of particle size and air flow distribution characteristics of the racemic mixture of formoterol, the distribution of the compound into the smaller bronchioles is limited, which results in a decreased effectiveness of the compound.

It is therefore desirable to find a compound with the therapeutic characteristics of formoterol which would not have the above described disadvantages.

## SUMMARY OF THE INVENTION

It has now been discovered that the (R,R) isomer of formoterol is an effective bronchodilator that does not have certain adverse effects associated with the administration of the racemic mixture of (R,R) and (S,S) formoterol. The present invention includes administering to a human (R,R) formoterol to cause bronchodilation and to decrease said adverse effects. Furthermore, it has also been discovered that by administering only the (R,R) isomer of formoterol there is decreased tolerance and hypersensitivity to the compound, relative to that seen when the racemic mixture of formoterol is administered. In addition, it has been discovered that by administering the (R,R) isomer of formoterol by inhalation, it is possible to obtain improved distribution of the compound in the smaller bronchioles which results in an increased bronchodilating effect. In addition, an increased duration of the beneficial effects is observed upon administration of the substantially pure (R,R) enantiomer, as compared to administration of the racemic drug.

The present invention also includes novel compositions of matter containing optically pure (R,R) formoterol which is useful as a bronchodilator. These novel compositions also avoid the above described adverse effects, increased toler-

ance or limited pattern of distribution when administered by inhalation, associated with the racemic mixture of formoterol.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses a method of eliciting a bronchodilator effect while avoiding the concomitant liability of adverse effects, development of tolerance, or limited pattern of bronchial distribution when administered by inhalation, which comprises administering to a human in need of bronchodilation an amount sufficient to alleviate bronchospasms, but insufficient to cause said adverse effects, development of tolerance, hypersensitivity or limited pattern of bronchial distribution when administered by inhalation, of (R,R) formoterol or a pharmaceutically acceptable salt thereof, substantially free of its (S,S) stereoisomer. The bronchodilator effects are achieved by utilizing the highly potent g-adrenergic effects of the (R,R) isomer of formoterol while substantially limiting the adverse effects, development of tolerance, hypersensitivity or limited pattern of bronchial distribution when administered by inhalation, by decreasing or eliminating the amount of (S,S) isomer in the composition.

As hereinbefore described in relation to formula I, Cl in the eutomer of Group 1.3 drugs characteristically has the (R) configuration. In the case of Group 1.3 drugs having two asymmetric carbon atoms, the eutomer could thus be the (R,R) or (R,S) isomer. Although we have found that it is the (R,R) enantiomer which has the greatest bronchodilator potency, Group 1.3 drugs having two asymmetric carbon atoms have hitherto been used in the clinic generally in the form of the (RS,RS) racemic mixture.

The present invention also encompasses a bronchodilator composition for the treatment of a patient in need of bronchodilating therapy which comprises an amount sufficient to alleviate bronchospasms but insufficient to cause adverse effects, development of tolerance or limited bronchial distribution when administered by inhalation, of (R,R) formoterol or a pharmaceutically acceptable salt thereof, substantially free of its (S,S) stereoisomer.

The racemic mixture of formoterol causes bronchial smooth muscle relaxation and modulates inhibition of mediator release effect; however, this racemic mixture causes adverse effects, leads to the development of tolerance and the development of hypersensitivity and results in a limited pattern of bronchial distribution when administered by inhalation. Utilizing the (R,R) isomer of formoterol results in diminished adverse effects, decreased development of tolerance and increased bronchial distribution when the compound is administered by inhalation. Thus, it is much more desirable to use the (R,R) isomer of formoterol when treating asthma, bronchitis, emphysema or to alleviate bronchospasms.

Furthermore, although there is some variability from one patient to another, it is generally observed that, by administering an effective amount of only the (R,R) isomer of formoterol it is possible to accomplish a more "targeted" therapy. A more "targeted" therapy means that by using the (R,R) isomer the compound's activity can be taken advantage of without also having consequences of the pharmacologic effects of the (S,S) isomer which are observed upon administration of the racemic mixture. This is important since it is not desirable for all patients to be administered a compound with such a multifaceted spectrum of activity.

The present invention provides a method or use for the treatment of inflammatory airways disease, in particular for effecting bronchodilatation, e.g. as a means of alleviating airways obstruction, in particular acute airways obstruction, e.g. asthma attack, occurring in such disease. The invention thus provides symptomatic, rather than prophylactic, therapy for such disease. The teaching of the present invention is applicable in the therapy of inflammatory or obstructive airways disease, in particular any such disease for which Group 1.3 drug therapy is commonly practiced, for example chronic obstructive pulmonary disease, e.g. consequential to cystic fibrosis, emphysema and, especially, chronic bronchitis and, most especially, asthma.

The present invention avoids deleterious side effects hereinbefore resulting or observed in, e.g. asthmatic, patients consequent to conventional clinical usage of Group 1.3 drugs as racemic mixtures. In particular the invention provides means to avoid, ameliorate or restrict deleterious side effects, e.g. side effects deleterious to the airways. Thus the invention provides means to avoid, ameliorate or restrict exacerbation of disease status, for example basal disease, e.g. basal asthmatic, status or to avoid, ameliorate or restrict compromise or deterioration of lung function, or any other side effect concomitant to conventional clinical usage, for example "anomalous", "rebound" or "paradoxical" bronchospasm and, especially, increase in airway obstruction, exacerbation of late asthmatic response or non-specific bronchial reactivity or arterial hypoxemia. Without limiting the present invention to any specific theory or mode of action, the present invention is in particular to be understood as providing a means for the avoidance, amelioration or restriction of exacerbation of airways hyperreactivity and/or of an inflammatory or other event associated with, or which is an etiological component of, inflammatory or obstructive airways disease, e.g. asthma. Such events are to be understood as including for example, inflammatory cell infiltration of the lungs or airways, connective tissue deposition or smooth muscle hyperplasia within the lungs or airways or other morphological change associated with asthmatic status. The present invention also provides a means of preventing or reducing morbidity, e.g. asthma morbidity, ascribable to conventional, e.g. high dosage or long term, Group 1.3 drug usage.

The present invention is especially applicable in the therapy of bronchial asthma of whatever type or genesis. It is applicable to both intrinsic and extrinsic asthma. It is especially applicable to the treatment of allergic or atopic (i.e. IgE-mediated) asthma or non-atopic asthma, as well as exercise induced asthma, occupational asthma, asthma induced following bacterial infection or drug, e.g. aspirin, ingestion and other non-allergic asthmas. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting chronic cough or wheezing symptoms, in particular at night, and diagnosed or diagnosable as "wheezy infants", i.e. as embracing the treatment of "wheezy infant syndrome". other diseases to which the present invention is in particular applicable include for example chronic obstructive pulmonary or airways disease (COPD or COAD).

The term "adverse effects" includes but is not limited to hand tremors, muscle tremors, nervousness, palpitations, tachycardia, increased heart rate, dyspnea, coughing, chest pain, chest discomfort, drying or irritation of the oropharynx and wheezing. Also included in the term "adverse effects" are headaches, dizziness, fatigue, hoarseness, backaches, nausea, vomiting, drowsiness, weakness, flushed feeling, sweating, unusual taste, muscle cramps, weakness, angina, vertigo, central stimulation, hypersensitivity and insomnia.

The term "substantially free of the (S,S) stereoisomer" as used herein means that the composition contains at least

about 90% by weight of (R,R) formoterol and 10% or less by weight of (S,S) formoterol. In a more preferred embodiment the composition contains at least 99% by weight (R,R) formoterol and 1% or less of (S,S) formoterol. In the most preferred embodiment the composition contains greater than 99% by weight of (R,R) formoterol and less than 1% by weight of (S,S) formoterol.

The term "eliciting a bronchodilator effect" means relief from the symptoms associated with obstructive airway diseases, which include but are not limited to respiratory distress, wheezing, coughing, shortness of breath, tightness or pressure in the chest and the like.

The term "development of tolerance" means that when administering the racemic mixture of formoterol in repeated dosage or over a period of time, the amount of the compound given to the patient must be increased in order to achieve the same effect as the lower dosage given at an earlier time.

The term "limited pattern of bronchial distribution when administered by inhalation" means that therapeutically efficacious quantities cannot penetrate into smaller bronchioles.

The mixture of formoterol isomers can be prepared according to U.S. Pat. No. 3,994,974. The diasteromers may be separated as described by Murase et al. [*Chem. Pharm. Bull.* 25, 1368-13 (1977). The individual isomers of formoterol may be obtained as described by Trofast et al. (op. cit.) by stereocontrolled synthesis from optically active starting material or by resolution of a mixture of enantiomers (i.e., the racemic mixture) using conventional means, such as an optically active resolving acid. Other standard methods of resolution known to those skilled in the art including but not limited to simple crystallization and chromatographic resolution can be used. (See for example, *Stereochemistry of Carbon Compounds*, E. L. Eliel, McGraw Hill 1962; "Tables of Resolving Agents," S. A. Wilen and Lochmuller, L. H. et al., 1975, *J. Chromatogr.* 113(3): 283–302.) Additionally, the optically pure (R,R) isomer can be prepared from the racemic mixture by enzymatic biocatalytic resolution. See, for example, U.S. Pat. Nos. 5,057,427 and 5,077,217, the disclosures of which are incorporated herein by reference.

The magnitude of a prophylactic or therapeutic dose of (R,R) formoterol in the acute or chronic management of disease will vary with the severity of the condition to be treated, and the route of administration. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose ranges when administered by inhalation, for the conditions described herein, is from about 1 μg to about 100 μg, in single or divided doses. Preferably, a daily dose range should be between about 6 μg to about 25 μg, in single or divided doses, while most preferably, a daily dose range should be between about 12 μg to about 25 μg, in from two to four divided doses. In managing the patient, the therapy should be initiated at a lower dose, perhaps about 3 μg to about 12 μg, and increased up to about 2×12 μg or higher depending on the patient's global response. When administered orally, preferably as a tablet, the preferred dose range is from 0.1 to 1.0 mg per day. It is further recommended that children, and patients over 65 years, and those with impaired renal, or hepatic function, initially receive low doses, and that they be titrated based on individual responses) and blood level(s). It may be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician would know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response.

The terms "an amount sufficient to alleviate bronchospasms but insufficient to cause said adverse effects" are encompassed by the above-described dosage amounts and dose frequency schedule.

Any suitable route of administration may be employed for providing the patient with an effective dosage of (R,R) formoterol. For example, oral, rectal, parenteral (subcutaneous, intramuscular, intravenous), transdermal, and like forms of administration may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, patches, and the like.

The pharmaceutical compositions of the present invention comprise (R,R) formoterol as the active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients.

The term "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable non-toxic acids including inorganic acids and organic acids. Suitable pharmaceutically acceptable acid addition salts for the compound of the present invention include acetic, benzenesulfonic (besylate), benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, and the like. The fumaric acid salt is particularly preferred.

The compositions of the present invention include compositions such as suspensions, solutions and elixirs; aerosols; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like. The compositions include compositions suitable for oral, rectal, parenteral (including subcutaneous, transdermal, intramuscular, and intravenous) and inhalation, although the most suitable route in any given case will depend on the condition being treated and the nature and severity of that condition. The most preferred routes of the present invention are: (1) oral by either tablets or capsules, (2) inhalation and (3) transdermal by patch. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled release means and/or delivery devices such as those described in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, the disclosures of which are hereby incorporated by reference.

The invention is further defined by reference to the following examples describing in detail the pharmacological characterization of the compound, and the preparation of compositions of the present invention. It will be apparent to those skilled in the art, that many modifications, both to materials, and methods, may be practiced without departing from the purpose and interest of this invention.

## EXAMPLES

### Procedure 1

β-Adrenergic Receptor Phosphorylation by β-Adrenoreceptor Kinase. Reconstituted β-adrenergic receptor is incubated with β-adrenoreceptor kinase in a buffer containing 20 mM Tris-HCl, pH 7.5, 2 mM EDTA, 20 mM NaCl, 6 mM $MgCl_2$, 6 mM sodium phosphate, 0.5 mM ascorbic acid 60 μM [$\gamma^{-32}$P]ATP at 30° C. The incubations

also contain varying concentrations of one of the following: buffer (control), (−)-isoproterenol, R,R-formoterol, S,S-formoterol or racemic formoterol. The incubations are stopped by the addition of SDS sample buffer followed by electrophoresis on 10% homogeneous polyacrylamide gels. Stoichiometries of phosphorylation are determined by cutting and counting the dried gel as described in Benovic J. L. et al. [*J. Biol. Chem.* 9026–9032 (1987)].

Procedure 2

Purification of component proteins. The β-adrenergic receptor from hamster lung is purified to >95% homogeneity by sequential affinity chromatography and high performance liquid chromatography as described by Benovic et al. [*Biochemistry* 23, 4510–4518 (1984)]. The stimulatory guanine nucleotide regulatory protein is purified from membranes derived from bovine cerebral cortex. The membranes, solubilized with 1% cholate, are centrifuged and the resulting supernatant chromatographed on DEAE-Sephacel, Ultrogel AcA34, octyl-Sepharose, and hydroxyapatite, with a final step on DEAE-Sephacel, as adapted from Strittmater and Neer [*Proc. Natl. Acad. Sci.* 77, 6344–6348 (1980)]. The resulting protein should be 50–90% pure by Coomassie Blue staining of polyacrylamide gels. The catalytic moiety of adenylate cyclase is solubilized from bovine caudate with sodium cholate and isolated from the other components of the system by Sepharose 6B chromatography as described in Strittmater and Neer (op. cit.). β-Adrenoreceptor kinase is purified from bovine cerebral cortex. The tissue is homogenized, and the resulting high speed supernatant fraction is precipitated with 13–26% ammonium sulfate. This material is then chromatographed on Ultrogel AcA34, DEAE-Sephacel, and CM-Fractogel. The preparations used should be 10–20% pure as judged by Coomassie Blue staining of SDS-polyacrylamide gels.

Assay for adenylate cyclase activity. The co-reconstitution of the purified proteins is carried out as described in Cerione et al. *J. Biol. Chem.* 259, 9979–9982 (1984). The pelleted proteins are incubated for 15 min. at 37° C. in 30 mM Tris-HCl, pH 7.5 containing 1 mM ATP, 2 μCi of [α-$^{32}$P]ATP 0.14 mM cAMP, 100 mM sucrose, 0.4 mM dithiothreitol, 2.8 mM phosphoenol pyruvate, 5.2 μg/mL pyruvate kinase, 10 μg/ml of myokinase, 5 mM $MgCl_2$, and varying concentrations of racemic formoterol, (R,R) formoterol and (S,S) formoterol (total volume=0.5 mL). The reaction is stopped by the addition of 0.25 mL 2% sodium dodecylsulfate containing 40 mM ATP and 1.4 m.M cAMP at pH 7.5. Water (0.5 mL) is added to each reaction tube and the contents placed on a Dowex 50AG WX4 resin. The eluate from the columns plus two successive water washes (1.0 mL) are discarded. The columns are then eluted with 3 mL water and the eluates collected in test tubes. Each fraction is diluted with 0.2 mL of 1.5 M imidazole HCl, pH 7.2. The tubes from each concentration (run in triplicate) are combined and decanted into columns containing 0.6 g neutral alumina that has been previously washed with 0.1 M imidazole HCl, pH 7.5. The eluate is collected in scintillation vials containing 12 mL Aquasol®. After the columns are completely drained, they are washed with an additional 1 mL of 0.1 M imidazole HCl, pH 7.5 which is collected in the same scintillation vials. The concentration of $^{32}$P-cAMP is determined in each sample.

The metabolic rates of the racemate and the isomers of formoterol have been studied in human liver tissues. It was unexpectedly found that the metabolic rate is significantly slower for (R,R) formoterol than for the racemate and for the SS-isomer. These new findings show that the clearance ($V_{max}/K_m$) was 152 for (R,R) formoterol, 381 for (S,S) formoterol and 489 for (R,R/S,S) formoterol. It is possible to calculate the relative biological half-lives ($t_{1/2}$) of the RR-isomer and the racemate from these data, using the formula $Cl=Vd\times 0.693/t_{1/2}$. Assuming the same distribution volume [Vd=1] for all three compounds, the relative half-lives are 4.6 for (R,R) formoterol and 1.4 for (R,R/S,S) formoterol. Thus, the half-life of (R,R) formoterol is approximately three times longer than the half-life of the racemate. This demonstrates a significant advantage of the pure RR enantiomer in terms of its duration of action as well as diminution of side effects.

Example 1

ORAL FORMULATION
Tablets:

| Formula | Quantity per Tablet (mg.) A | B |
|---|---|---|
| (R,R) formoterol | 0.12 | 0.25 |
| Lactose | 41.38 | 41.25 |
| Cornstarch | 3.0 | 3.0 |
| Water (per thousand Tablets)* | 30.0 ml | 30.0 ml |
| Cornstarch | 5.00 | 5.00 |
| Magnesium Stearate | 0.50 | 0.50 |
| | 50.00 | 50.00 |

*The water evaporates during manufacture

The formoterol is blended with the lactose until a uniform blend is formed. The smaller quantity of cornstarch is blended with the water to form the resulting cornstarch paste. This is then mixed with said uniform blend until a uniform wet mass is formed. The remaining cornstarch is added to the resulting wet mass and mixed until uniform granules are obtained. The granules are then screened through a suitable milling machine, using a 1/4 inch stainless steel screen. The milled granules are then dried in a suitable drying oven until the desired moisture content is obtained. The dried granules are then milled through a suitable milling machine, using 1/4 mesh stainless steel screen. The magnesium stearate is then blended and the resulting mixture is compressed into tablets of desired shape, thickness, hardness and disintegration.

Example 2

ORAL INHALATION

| Formula | Quantity contained in Each Metered Dose Dispenser 7.5 mL (10.5 g) Canister |
|---|---|
| (R,R) formoterol | 1.8 mg |
| trichloromonofluoromethane | 5.16 g |
| dichlorodifluoromethane | 5.16 g |
| sorbitan trioleate | 0.105 g |

The metered dose dispenser contains micronized (R,R) formoterol fumarate dihydrate in suspension. Each actuation delivers 6 μg of (R,R) formoterol fumarate dihydrate from the mouthpiece. Each canister provides about 300 inhalations.

What is claimed is:

1. A method of treating asthma in human, the method comprising administering to the human a therapeutically effective amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof.

2. The method according to claim 1, wherein the amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof, is administered orally, transdermally, by inhalation, by subcutaneous injection or by intravenous infusion.

3. The method according to claim 2, wherein the amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof, is administered by inhalation at a dosage of about 1 μg to about 100 μg per day.

4. The method according to claim 3, wherein the amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof, is administered is about 6 μg to about 25 μg per day.

5. The method according to claim 3, wherein the formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, comprises formoterol fumarate dihydrate.

6. The method according to claim 5, wherein the formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, comprises formoterol fumarate dihydrate.

7. A method of treating or preventing bronchospasm in a human, the method comprising administering to the human a therapeutically effective amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof.

8. The method according to claim 7, wherein the amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof, is administered orally, transdermally, by inhalation, by subcutaneous injection or by intravenous infusion.

9. The method according to claim 8, wherein the amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof, is administered by inhalation at a dosage of about 1 μg to about 100 μg per day.

10. The method according to claim 9, wherein the amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof, is administered is about 6 μg to about 25 μg per day.

11. The method according to claim 9, wherein the formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, comprises formoterol fumarate dihydrate.

12. The method according to claim 11, wherein the formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, comprises formoterol fumarate dihydrate.

13. A method of eliciting bronchodilation effect in a human, the method comprising administering to the human a therapeutically effective amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof.

14. The method according to claim 13, wherein the amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof, is administered orally, transdermally, by inhalation, by subcutaneous injection or by intravenous infusion.

15. The method according to claim 14, wherein the amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof, is administered by inhalation at a dosage of about 1 μg to about 100 μg per day.

16. The method according to claim 15, wherein the amount of formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, or a pharmaceutically acceptable salt thereof, is administered is about 6 μg to about 25 μg per day.

17. The method according to claim 15, wherein the formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, comprises formoterol fumarate dihydrate.

18. The method according to claim 17, wherein the formoterol containing at least 90% by weight (R,R)-formoterol and 10% or less by weight (S,S)-formoterol, comprises formoterol fumarate dihydrate.

* * * * *

B

# Patent Assignment Abstract of Title

***NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.***

**Total Assignments: 1**

**Patent #:** 5795564 **Issue Dt:** 08/18/1998 **Application #:** 08613382 **Filing Dt:** 03/07/1996

**Inventors:** GUNNAR ABERG, JOHN MORLEY

**Title:** METHODS AND COMPOSITIONS FOR TREATING PULMONARY DISORDERS USING OPTICALLY PURE (R,R)-FORMOTEROL

**Assignment: 1**

**Reel/Frame:** 008018 / 0813 **Recorded:** 07/05/1996 **Pages:** 4

**Conveyance:** ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

**Assignors:** ABERG, GUNNAR **Exec Dt:** 06/20/1996

MORLEY, JOHN **Exec Dt:** 06/24/1996

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**ABERG, Gunnar**
**MORLEY, John**

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies):

Name: **Sepracor, Inc.**

Internal Address: _____

Street Address: **33 Locke Drive**

City: **Marlborough** State: **MA** ZIP: **01752**

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:

☒ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other _____

Execution Date: **June 20, 1996 and June 24, 1996**

4. Application number(s) or registration numbers(s):

If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No.(s)

**08/613,382**

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: **Philip E. Hansen, Ph.D.**

Internal Address: _____

Street Address: **Heslin & Rothenberg, P.C.**

**5 Columbia Circle**

City: **Albany** State: **NY** ZIP: **12205**

6. Total number of applications and patents involved: **1**

7. Total fee (37 CFR 3.41):.....$ **40.00**

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*To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.*

**Philip E. Hansen** _____ **July 2, 1996**

Name of Person Signing Signature Date

Total number of pages including cover sheet, attachments, and document: **4**

MKD 7-5-96

ASSIGNMENT

WHEREAS, We, GUNNAR ABERG, a citizen of Sweden and JOHN MORLEY, a citizen of Great Britain, residing at 6 Brickyard Lane, Westborough, Massachusetts 01681 and 13 Kenmore Close, Kent Road, Kew, Richmond-upon-Thames, United Kingdom, respectively, have invented certain new and useful improvements in METHODS AND COMPOSITIONS FOR TREATING PULMONARY DISORDERS USING OPTICALLY PURE (R,R)-FORMOTEROL, for which We have executed an application for Letters Patent of the United States, Serial Number 08/613,382, filed March 7, 1996; and

WHEREAS, Sepracor, Inc. having offices at 33 Locke Drive, Marlborough, Massachusetts 01752, is desirous of obtaining the entire right, title and interest in, to and under the said improvements and the said application;

NOW, THEREFORE, in consideration of the sum of One Dollar ($1.00) to us in hand paid, and other good and valuable consideration, the receipt of which is hereby acknowledged, We the said Gunnar Aberg and John Morley have sold, assigned, transferred and set over, and by these presents do hereby sell, assign, transfer and set over, unto the said Sepracor, Inc., its successors, legal representatives and assigns, the entire right, title and interest in, to and under the said improvements, and the said provisional application, all non-provisional applications arising therefrom, and all divisions, renewals and continuations thereof, and all Letters Patent which may be granted thereon and all reissues and extensions thereof, and all applications for Letters Patent which may hereafter be filed for said improvements in any country or countries foreign to the United States, and all Letters Patent which may be granted for said improvements in any country or countries foreign to the United States and all extensions, renewals and reissues thereof; and We hereby authorize and request the Commissioner of Patents of the United States, and any Official of any country or countries foreign to the United States, whose duty it is to issue patents on applications as aforesaid, to issue all Letters Patent for said improvements to the said Sepracor, Inc., its successors, legal representatives and assigns, in accordance with the terms of this instrument.

AND WE HEREBY covenant that We have full right to convey the entire interest herein assigned, and that We have not executed, and will not execute, any agreement in conflict herewith.

AND WE HEREBY further covenant and agree that We will communicate to the said Sepracor, Inc., its successors, legal representatives and assigns, any facts known to us respecting said improvements, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuing and reissue applications, make all rightful oaths and generally do everything

possible to aid the said Sepracor, Inc., its successors, legal representatives and assigns, to obtain and enforce proper patent protection for said improvements in all countries.

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 20th day of June, 1996.

GUNNAR ABERG

STATE OF MASSACHUSETTS )
) ss.:
COUNTY OF Middlesex )

On this 20th day of June, 1996, before me personally came GUNNAR ABERG, to me known and known to me to be the person of that name, who signed and sealed the foregoing instrument, and he acknowledged the same to be his free act and deed.

Notary Public

LINDA S. KING
Notary Public
My Commission Expires June 21, 2002

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 24 day of June, 1996.

JOHN MORLEY

Witness

Witness

# BROVANA™

# (arformoterol tartrate) Inhalation Solution

# 15 mcg*/2 mL

*potency expressed as arformoterol

**For oral inhalation only**

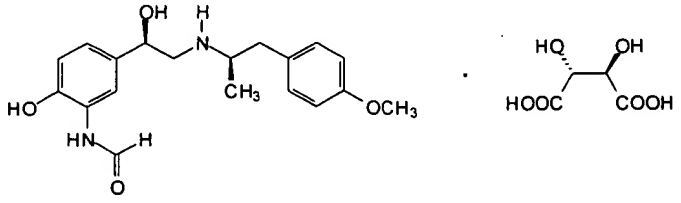
**WARNING:**

**Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol may apply to arformoterol (a long-acting beta$_2$-adrenergic agonist), the active ingredient in BROVANA (see WARNINGS).**

## DESCRIPTION

BROVANA (arformoterol tartrate) Inhalation Solution is a sterile, clear, colorless, aqueous solution of the tartrate salt of arformoterol, the (R,R)-enantiomer of formoterol.

Arformoterol is a selective beta$_2$-adrenergic bronchodilator. The chemical name for arformoterol tartrate is formamide, N-[2-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-, (2R,3R)-2,3-dihydroxybutanedioate (1:1 salt), and its established structural formula is as follows:




The molecular weight of *arformoterol tartrate* is 494.5 g/mol, and its empirical formula is $C_{19}H_{24}N_2O_4 \cdot C_4H_6O_6$ (1:1 salt). It is a white to off-white solid that is slightly soluble in water.

Arformoterol tartrate is the United States Adopted Name (USAN) for (R,R)-formoterol L-tartrate.

BROVANA is supplied as 2 mL of arformoterol tartrate solution packaged in 2.1 mL unit-dose, low-density polyethylene (LDPE) vials. Each unit-dose vial contains 15 mcg of arformoterol (equivalent to 22 mcg of arformoterol tartrate) in a sterile, isotonic saline solution, pH-adjusted to 5.0 with citric acid and sodium citrate.

BROVANA requires no dilution before administration by nebulization. Like all other nebulized treatments, the amount delivered to the lungs will depend upon patient factors, the nebulizer used, and compressor performance. Using the PARI LC PLUS® nebulizer (with mouthpiece) connected to a PARI DURA-NEB® 3000 compressor under *in vitro* conditions, the mean delivered dose from the mouthpiece (% nominal) was approximately 4.1 mcg (27.6%) at a mean flow rate of 3.3 L/min. The mean nebulization time was 6 minutes or less. BROVANA should be administered from a standard jet nebulizer at adequate flow rates via face mask or mouthpiece (see **Dosage and Administration**).

Patients should be carefully instructed on the correct use of this drug product (please refer to the accompanying **Medication Guide**).

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Arformoterol, the (R,R)-enantiomer of formoterol, is a selective long-acting $beta_2$-adrenergic receptor agonist ($beta_2$-agonist) that has two-fold greater potency than racemic formoterol (which contains both the (S,S) and (R,R)-enantiomers). The (S,S)-enantiomer is about 1,000-fold less potent as a $beta_2$-agonist than the (R,R)-enantiomer. While it is recognized that $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the heart, data indicate that there are also $beta_2$-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including arformoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic AMP). Increased intracellular cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

*In vitro* tests show that arformoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Arformoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these *in vitro* and animal findings to humans is unknown.

## Animal Pharmacology

In animal studies investigating its cardiovascular effects, arformoterol induced dose-dependent increases in heart rate and decreases in blood pressure consistent with its pharmacology as a beta-adrenergic agonist. In dogs, at systemic exposures higher than anticipated clinically, arformoterol also induced exaggerated pharmacologic effects of a beta-adrenergic agonist on cardiac function as measured by electrocardiogram (sinus tachycardia, atrial premature beats, ventricular escape beats, PVCs).

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

## Pharmacokinetics

The pharmacokinetics (PK) of arformoterol have been investigated in healthy subjects, elderly subjects, renally and hepatically impaired subjects, and chronic obstructive pulmonary disease (COPD) patients following the nebulization of the recommended therapeutic dose and doses up to 96 mcg.

## Absorption

In COPD patients administered 15 mcg arformoterol every 12 hours for 14 days, the mean steady-state peak (R,R)-formoterol plasma concentration ($C_{max}$) and systemic exposure ($AUC_{0\text{-}12h}$) were 4.3 pg/mL and 34.5 pg*hr/mL, respectively. The median steady-state peak (R,R)-formoterol plasma concentration time ($t_{max}$) was observed approximately one half hour after drug administration.

Systemic exposure to (R,R)-formoterol increased linearly with dose in COPD patients following arformoterol doses of 5 mcg, 15 mcg, or 25 mcg twice daily for 2 weeks or 15 mcg, 25 mcg, or 50 mcg once daily for 2 weeks.

In a crossover study in patients with COPD, when arformoterol 15 mcg inhalation solution and 12 and 24 mcg formoterol fumarate inhalation powder (Foradil® Aerolizer™) was administered twice daily for 2 weeks, the accumulation index was approximately 2.5 based on the plasma (R,R)-formoterol concentrations in all three treatments. At steady state, geometric means of systemic exposure ($AUC_{0\text{-}12h}$) to (R,R)-formoterol following 15 mcg of arformoterol inhalation solution and 12 mcg of formoterol fumarate inhalation powder were 39.33 pg*hr/mL and 33.93 pg*hr/mL, respectively (ratio 1.16; 90% CI 1.00, 1.35), while the geometric means of the $C_{max}$ were 4.30 pg/mL and 4.75 pg/mL, respectively (ratio 0.91; 90% CI 0.76, 1.09).

In a study in patients with asthma, treatment with arformoterol 50 mcg with pre- and post-treatment with activated charcoal resulted in a geometric mean decrease in (R,R)-formoterol $AUC_{0\text{-}6h}$ by 27% and $C_{max}$ by 23% as compared to treatment with arformoterol 50 mcg alone. This suggests that a substantial portion of systemic drug exposure is due to pulmonary absorption.

## Distribution

The binding of arformoterol to human plasma proteins in vitro was 52-65% at concentrations of 0.25, 0.5 and 1.0 ng/mL of radiolabeled arformoterol. The concentrations of arformoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of multiple doses of 50 mcg arformoterol.

## Metabolism

*In vitro* profiling studies in hepatocytes and liver microsomes have shown that arformoterol is primarily metabolized by direct conjugation (glucuronidation) and secondarily by O-demethylation. At least five human uridine diphosphoglucuronosyltransferase (UGT) isozymes catalyze arformoterol glucuronidation *in vitro*. Two cytochrome P450 isozymes (CYP2D6 and secondarily CYP2C19) catalyze the O-demethylation of arformoterol.

Arformoterol did not inhibit CYP1A2, CYP2A6, CYP2C9/10, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or CYP4A9/11 enzymes at >1,000-fold higher concentrations than the expected peak plasma concentrations following a therapeutic dose.

Arformoterol was almost entirely metabolized following oral administration of 35 mcg of radiolabeled arformoterol in eight healthy subjects. Direct conjugation of arformoterol with glucuronic acid was the major metabolic pathway. Most of the drug-related material in plasma and urine was in the form of glucuronide or sulfate conjugates of arformoterol. O-Desmethylation and conjugates of the O-desmethyl metabolite were relatively minor metabolites accounting for less than 17% of the dose recovered in urine and feces.

## Elimination

After administration of a single oral dose of radiolabeled arformoterol to eight healthy male subjects, 63% of the total radioactive dose was recovered in urine and 11% in feces within 48 hours. A total of 89% of the total radioactive dose was recovered within 14 days, with 67% in urine and 22% in feces. Approximately 1% of the dose was recovered as unchanged arformoterol in urine over 14 days. Renal clearance was 8.9 L/hr for unchanged arformoterol in these subjects.

In COPD patients given 15 mcg inhaled arformoterol twice a day for 14 days, the mean terminal half-life of arformoterol was 26 hours.

## Special Populations

### Gender

A population PK analysis indicated that there was no effect of gender upon the pharmacokinetics of arformoterol.

### Race

The influence of race on arformoterol pharmacokinetics was assessed using a population PK analysis and data from healthy subjects. There was no clinically significant impact of race upon the pharmacokinetic profile of arformoterol.

### Geriatric

The pharmacokinetic profile of arformoterol in 24 elderly subjects (aged 65 years or older) was compared to a younger cohort of 24 subjects (18-45 years) that were matched for body weight and gender. No significant differences in systemic exposure (AUC and $C_{max}$) were observed when the two groups were compared.

### Pediatric

The pharmacokinetics of arformoterol have not been studied in pediatric subjects.

### Hepatic Impairment

The pharmacokinetic profile of arformoterol was assessed in 24 subjects with mild, moderate, and severe hepatic impairment. The systemic exposure ($C_{max}$ and AUC) to arformoterol increased 1.3 to 2.4-fold in subjects with hepatic impairment compared to 16 demographically matched healthy control subjects. No clear relationship between drug exposure and the severity of hepatic impairment was observed. BROVANA should be used cautiously in patients with hepatic impairment.

### Renal Impairment

The impact of renal disease upon the pharmacokinetics of arformoterol was studied in 24 subjects with mild, moderate, or severe renal impairment. Systemic exposure (AUC and $C_{max}$) to arformoterol was similar in renally impaired patients compared with demographically matched healthy control subjects.

## Pharmacogenetics

Arformoterol is eliminated through the action of multiple drug metabolizing enzymes. Direct glucuronidation of arformoterol is mediated by several UGT enzymes and is the primary elimination route. O-Desmethylation is a secondary route catalyzed by the CYP enzymes CYP2D6 and CYP2C19. In otherwise healthy subjects with reduced CYP2D6 and/or UGT1A1 enzyme activity, there was no impact on systemic exposure to arformoterol compared to subjects with normal CYP2D6 and/or UGT1A1 enzyme activities.

## Pharmacodynamics

### Systemic Safety and Pharmacokinetic/ Pharmacodynamic Relationships

The predominant adverse effects of inhaled $beta_2$-agonists occur as a result of excessive activation of systemic beta-adrenergic receptors. The most common adverse effects may include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma potassium, and increases in plasma glucose.

Effects on Serum Potassium and Serum Glucose Levels

Changes in serum potassium and serum glucose were evaluated in a dose ranging study of twice daily (5 mcg, 15 mcg, or 25 mcg; 215 patients with COPD) and once daily (15 mcg, 25 mcg, or 50 mcg; 191 patients with COPD) BROVANA in COPD patients. At 2 and 6 hours post dose at week 0 (after the first dose), mean changes in serum potassium ranging from 0 to –0.3 mEq/L were observed in the BROVANA groups with similar changes observed after 2 weeks of treatment. Changes in mean serum glucose

levels, ranging from a decrease of 1.2 mg/dL to an increase of 32.8 mg/dL were observed for BROVANA dose groups at both 2 and 6 hours post dose, both after the first dose and 14 days of daily treatment.

Electrophysiology

The effect of BROVANA on QT interval was evaluated in a dose ranging study following multiple doses of BROVANA 5 mcg, 15 mcg, or 25 mcg twice daily or 15 mcg, 25 mcg, or 50 mcg once daily for 2 weeks in patients with COPD. ECG assessments were performed at baseline, time of peak plasma concentration and throughout the dosing interval. Different methods of correcting for heart rate were employed, including a subject-specific method and the Fridericia method.

Relative to placebo, the mean change in subject-specific $QT_c$ averaged over the dosing interval ranged from -1.8 to 2.7 msec, indicating little effect of BROVANA on cardiac repolarization after 2 weeks of treatment. The maximum mean change in subject-specific $QT_c$ for the BROVANA 15 mcg twice daily dose was 17.3 msec, compared with 15.4 msec in the placebo group. No apparent correlation of $QT_c$ with arformoterol plasma concentration was observed.

**Electrocardiographic Monitoring in Patients with COPD**

The effect of different doses of BROVANA on cardiac rhythm was assessed using 24-hour Holter monitoring in two 12-week double-blind, placebo-controlled studies of 1,456 patients with COPD (873 received BROVANA at 15 or 25 mcg twice daily or 50 mcg once daily doses; 293 received placebo; 290 received salmeterol). The 24-hour Holter monitoring occurred once at baseline, and up to 3 times during the 12-week treatment period. The rates of new-onset cardiac arrhythmias not present at baseline over the double-blind 12-week treatment period were similar (approximately 33-34%) for patients who received BROVANA 15 mcg twice daily to those who received placebo. There was a dose-related increase in new, treatment emergent arrhythmias seen in patients who received BROVANA 25 mcg twice daily and 50 mcg once daily, 37.6% and 40.1 %, respectively. The frequencies of new treatment emergent events of non-sustained (3-10 beat run) and sustained (>10 beat run) ventricular tachycardia were 7.4% and 1.1% in BROVANA 15 mcg twice daily and 6.9% and 1.0% in placebo. In patients who received BROVANA 25 mcg twice daily and 50 mcg once daily the frequencies of non-sustained (6.2% and 8.2%, respectively) and sustained ventricular tachycardia (1.0% and 1.0%, respectively) were similar. Five cases of ventricular tachycardia were reported as adverse events (1 in BROVANA 15 mcg twice daily and 4 in placebo), with two of these events leading to discontinuation of treatment (2 in placebo).

There were no baseline occurrences of atrial fibrillation/ flutter observed on 24-hour Holter monitoring in patients treated with BROVANA 15 mcg twice daily or placebo. New, treatment emergent atrial fibrillation/ flutter occurred in 0.4% of patients who received BROVANA 15 mcg twice daily and 0.3% of patients who received placebo. There was a dose-related increase in the frequency of atrial fibrillation/ flutter reported in the BROVANA 25 mcg twice daily and 50 mcg once daily dose groups of 0.7% and 1.4%, respectively. Two cases of atrial fibrillation/ flutter were reported as adverse events (1 in BROVANA 15 mcg twice daily and 1 in placebo).

Dose-related increases in mean maximum change in heart rate in the 12 hours after dosing were also observed following 12 weeks of dosing with BROVANA 15 mcg twice daily (8.8 bpm), 25 mcg twice daily (9.9 bpm) and 50 mcg once daily (12 bpm) versus placebo (8.5 bpm).

### Tachyphylaxis/ Tolerance

In two placebo-controlled clinical trials in patients with COPD involving approximately 725 patients in each, the overall efficacy of BROVANA was maintained throughout the 12-week trial duration. However, tolerance to the bronchodilator effect of BROVANA was observed after 6 weeks of dosing, evidenced by a decrease in bronchodilator effect as measured by $FEV_1$. $FEV_1$ improvement at the end of the 12-hour dosing interval decreased by approximately one third (22.1% mean improvement after the first dose compared to 14.6% at week 12). Tolerance to the $FEV_1$ bronchodilator effect of BROVANA was not accompanied by other clinical manifestations of tolerance in these trials.

## CLINICAL TRIALS

### Adult COPD Trials

BROVANA (arformoterol tartrate) Inhalation Solution was studied in two identical, 12-week, double-blind, placebo- and active-controlled, randomized, multi-center, parallel group trials conducted in the United States (Clinical Trial A and Clinical Trial B). A total of 1,456 adult patients (age range: 34 to 89 years; mean age: 63 years) with COPD who had a mean $FEV_1$ of 1.3 L (42% of predicted) were enrolled in the two clinical trials. The diagnosis of COPD was based on a prior clinical diagnosis of COPD, a smoking history (greater than 15 pack-years), age (at least 35 years), spirometry results (baseline FEV1 $\leq$ 65% of predicted value and >0.70 L, and a $FEV_1$/ forced vital capacity (FVC) ratio $\leq$70%). About 80% of patients in these studies had bronchodilator reversibility, defined as a 10% or greater increase $FEV_1$ after inhalation of 2 actuations (180 mcg) racemic albuterol from a metered dose inhaler). Both trials compared BROVANA 15 mcg twice daily (288 patients), 25 mcg twice daily (292 patients), 50 mcg once daily (293 patients) with placebo (293 subjects). Both trials included salmeterol inhalation aerosol, 42 mcg twice daily as an active comparator (290 patients).

In both 12-week trials, BROVANA 15 mcg twice daily resulted in significantly greater post-dose bronchodilation (as measured by percent change from study baseline $FEV_1$ at the end of the dosing interval over the 12 weeks of treatment, the primary efficacy endpoint) compared to placebo. Compared to BROVANA 15 mcg twice daily, BROVANA 25 mcg twice daily and 50 mcg once daily did not provide sufficient additional benefit on a variety of endpoints, including $FEV_1$, to support the use of higher doses. Plots of the mean change in $FEV_1$ values obtained over the 12 hours after dosing for the BROVANA 15 mcg twice daily dose group and for the placebo group are provided in Figures 1 and 2 for Clinical Trial A, below. The plots include mean $FEV_1$ change observed after the first dose and after 12 weeks of treatment. The results from Clinical Trial B were similar.

**Figure 1** **Mean Change in $FEV_1$ Over Time for Clinical Trial A at Week 0 (Day 1)**

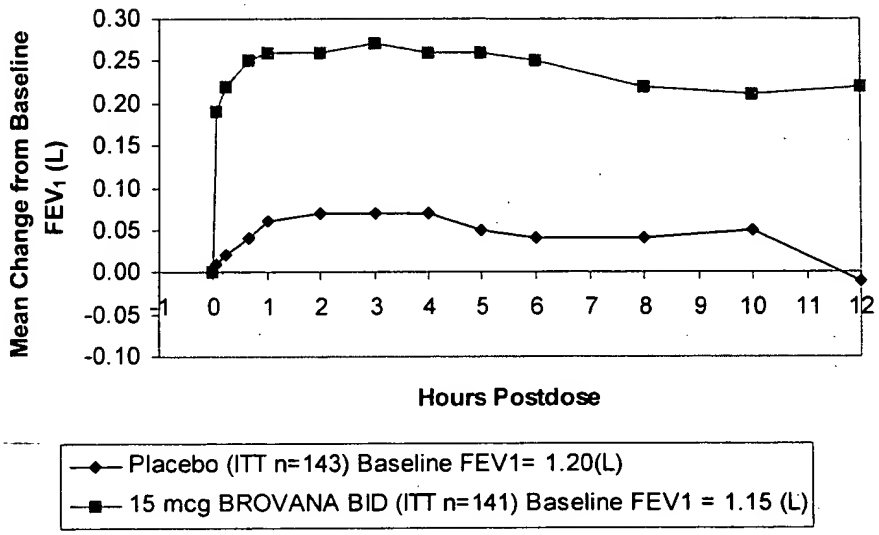



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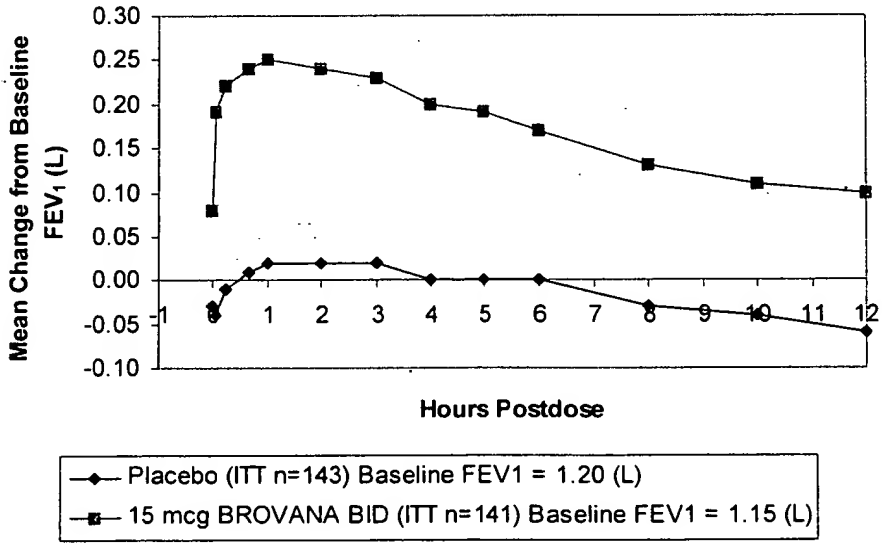
**Figure 2** **Mean Change in $FEV_1$ Over Time for Clinical Trial A at Week 12**

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271 BROVANA 15 mcg twice daily significantly improved bronchodilation compared to
272 placebo over the 12 hours after dosing ($FEV_1$ $AUC_{0\text{-}12h}$). This improvement was
273 maintained over the 12 week study period.

Following the first dose of BROVANA 15 mcg, the median time to onset of bronchodilation, defined by an $FEV_1$ increase of 15%, occurred at 6.7 min. When defined as an increase in $FEV_1$ of 12% and 200 mL, the time to onset of bronchodilation was 20 min after dosing. Peak bronchodilator effect was generally seen within 1-3 hours of dosing.

In both clinical trials, compared to placebo, patients treated with BROVANA demonstrated improvements in peak expiratory flow rates, supplemental ipratropium and rescue albuterol use.

## INDICATIONS AND USAGE

BROVANA (arformoterol tartrate) Inhalation Solution is indicated for the long term, twice daily (morning and evening) maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. BROVANA is for use by nebulization only.

## CONTRAINDICATIONS

BROVANA (arformoterol tartrate) Inhalation Solution is contraindicated in patients with a history of hypersensitivity to arformoterol, racemic formoterol or to any other components of this product.

## WARNINGS

- **Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death.**
    - A 28-week, placebo-controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death may represent a class effect of the long-acting beta$_2$-adrenergic agonists, including BROVANA. No study adequate to determine whether the rate of asthma related death is increased in patients treated with BROVANA has been conducted.
    - Clinical studies with racemic formoterol (Foradil® Aerolizer™) suggested a higher incidence of serious asthma exacerbations in patients who received racemic formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.
- **The studies described above enrolled patients with asthma. Data are not available to determine whether the rate of death in patients with COPD is increased by long-acting beta$_2$-adrenergic agonists.**
- **BROVANA is indicated for the long term, twice daily (morning and evening) maintenance treatment for bronchoconstriction in chronic obstructive**

**pulmonary disease (COPD), and is not indicated for the treatment of acute episodes of bronchospasm, i.e., rescue therapy.**

- **BROVANA should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. The use of BROVANA in this setting is inappropriate.**
- **BROVANA should not be used in children as the safety and efficacy of BROVANA have not been established in pediatric patients.**
- **BROVANA should not be used in conjunction with other inhaled, long-acting beta$_2$-agonists. BROVANA should not be used with other medications containing long-acting beta$_2$-agonists.**
- **When beginning treatment with BROVANA, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.**
- **See PRECAUTIONS, Information for Patients and the accompanying Medication Guide.**

### Paradoxical Bronchospasm

As with other inhaled beta$_2$-agonists, BROVANA can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, BROVANA should be discontinued immediately and alternative therapy instituted.

### Deterioration of Disease

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BROVANA no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta$_2$-agonist becomes less effective or the patient needs more inhalation of short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of BROVANA beyond the recommended 15 mcg twice daily dose is not appropriate in this situation.

### Cardiovascular Effects

BROVANA, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of BROVANA at the recommended dose, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. BROVANA, as with other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension (see **PRECAUTIONS, General**).

### Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of BROVANA as demonstrated by cases of anaphylactic reaction, urticaria, angioedema, rash and bronchospasm.

### Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. As with other inhaled beta$_2$-adrenergic drugs, BROVANA should not be used more often, at higher doses than recommended, or with other long-acting beta-agonists.

## PRECAUTIONS

### General

BROVANA (arformoterol tartrate) Inhalation Solution should not be used to treat acute symptoms of COPD. BROVANA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. When prescribing BROVANA, the physician should also provide the patient with an inhaled, short-acting beta$_2$-agonist for treatment of COPD symptoms that occur acutely, despite regular twice-daily (morning and evening) use of BROVANA. Patients should also be cautioned that increasing inhaled beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated (see **Information for Patients** and the accompanying **Medication Guide**).

BROVANA, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and/or diastolic blood pressure, pulse rate and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with arformoterol tartrate. Doses of the related beta$_2$-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Beta-agonist medications may produce significant hypokalemia in some patients, possibly though intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were infrequent during clinical studies with long-term administration of BROVANA at the recommended dose.

### Information for Patients

**Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill. The complete text of the Medication Guide is reprinted at the end of this document.** Patients should be given the following information:

1. Patients should be informed that long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death.

2. BROVANA is not indicated to relieve acute respiratory symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta$_2$-agonist (the health-care provider should prescribe the patient with such medication and instruct the patient in how it should be used). Patients should be instructed to seek medical attention if their symptoms worsen, if BROVANA treatment becomes less effective, or if they need more inhalations of a short-acting beta$_2$-agonist than usual. Patients should not inhale more than one dose at any one time. The daily dosage of BROVANA should not exceed one vial (15 mcg) by inhalation twice daily (30 mcg total daily dose).

3. Patients should be informed that treatment with beta$_2$-agonists may lead to adverse events which include palpitations, chest pain, rapid heart rate, tremor, or nervousness.

4. Patients should be instructed to use BROVANA by nebulizer only and not to inject or swallow this inhalation solution.

5. Patients should protect BROVANA single-use low-density polyethylene (LDPE) vials from light and excessive heat. The protective foil pouches should be stored under refrigeration between 2°C and 8°C (36°–46°F). They should not be used after the expiration date stamped on the container. Patients should be instructed that once the foil pouch is opened, the contents of the vial should be used immediately and to discard any vial if the solution is not colorless.

6. The drug compatibility (physical and chemical), efficacy and safety of BROVANA when mixed with other drugs in a nebulizer have not been established.

7. Women should be advised to contact their physician if they become pregnant or if they are nursing.

8. It is important that patients understand how to use the BROVANA appropriately and how it should be used in relation to other medications to treat COPD they are taking (see the accompanying Medication Guide and the Instructions for Using BROVANA).

## Drug Interactions

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the pharmacologically predictable sympathetic effects of BROVANA may be potentiated.

When paroxetine, a potent inhibitor of CYP2D6, was co-administered with BROVANA at steady-state, exposure to either drug was not altered. Dosage adjustments of BROVANA are not necessary when the drug is given concomitantly with potent CYP2D6 inhibitors.

Concomitant treatment with methylxanthines (aminophylline, theophylline), steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists.

The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened

by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of beta-agonists with non-potassium sparing diuretics.

BROVANA, as with other $beta_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the $QT_c$ interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the $QT_c$ interval have an increased risk of ventricular arrhythmias. The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving BROVANA has not been completely evaluated. In two combined 12-week placebo controlled trials that included BROVANA doses of 15 mcg twice daily, 25 mcg twice daily, and 50 mcg once daily, 54 of 873 BROVANA -treated subjects received concomitant theophylline at study entry. In a 12-month controlled trial that included a 50 mcg once daily BROVANA dose, 30 of the 528 BROVANA -treated subjects received concomitant theophylline at study entry. In these trials, heart rate and systolic blood pressure were approximately 2-3 bpm and 6-8 mm Hg higher, respectively, in subjects on concomitant theophylline compared with the overall population.

Beta-adrenergic receptor antagonists (beta-blockers) and BROVANA may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted in mice using oral administration and rats using inhalation administration to evaluate the carcinogenic potential of arformoterol.

In a 24-month carcinogenicity study in CD-1 mice, arformoterol caused a dose-related increase in the incidence of uterine and cervical endometrial stromal polyps and stromal cell sarcoma in female mice at oral doses of 1 mg/kg and above (AUC exposure approximately 70 times adult exposure at the maximum recommended daily inhalation dose).

In a 24-month carcinogenicity study in Sprague-Dawley rats, arformoterol caused a statistically significant increase in the incidence of thyroid gland c-cell adenoma and carcinoma in female rats at an inhalation dose of 200 mcg/kg (AUC exposure approximately 130 times adult exposure at the maximum recommended daily inhalation dose). There were no tumor findings with an inhalation dose of 40 mcg/kg (AUC exposure approximately 55 times adult exposure at the maximum recommended daily inhalation dose).

Arformoterol was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacteria, chromosome aberration analyses in mammalian cells, and micronucleus test in mice.

Arformoterol had no effects on fertility and reproductive performance in rats at oral doses up to 10 mg/kg (approximately 2700 times the maximum recommended daily inhalation dose in adults on a $mg/m^2$ basis).

## Pregnancy: Teratogenic Effects

### Pregnancy Category C

Arformoterol has been shown to be teratogenic in rats based upon findings of omphalocele (umbilical hernia), a malformation, at oral doses of 1 mg/kg and above (AUC exposure approximately 370 times adult exposure at the maximum recommended daily inhalation dose). Increased pup loss at birth and during lactation and decreased pup weights were observed in rats at oral doses of 5 mg/kg and above (AUC exposure approximately 1100 times adult exposure at the maximum recommended daily inhalation dose). Delays in development were evident with an oral dose of 10 mg/kg (AUC exposure approximately 2400 times adult exposure at the maximum recommended daily inhalation dose).

Arformoterol has been shown to be teratogenic in rabbits based upon findings of malpositioned right kidney, a malformation, at oral doses of 20 mg/kg and above (AUC exposure approximately 8400 times adult exposure at the maximum recommended daily inhalation dose). Malformations including brachydactyly, bulbous aorta, and liver cysts were observed at doses of 40 mg/kg and above (approximately 22,000 times the maximum recommended daily inhalation dose in adults on a $mg/m^2$ basis). Malformation including adactyly, lobular dysgenesis of the lung, and interventricular septal defect were observed at 80 mg/kg (approximately 43,000 times the maximum recommended daily inhalation dose in adults on a $mg/m^2$ basis). Embryolethality was observed at 80 mg/kg/day (approximately 43,000 times the maximum recommended daily inhalation dose in adults on a $mg/m^2$ basis). Decreased pup body weights were observed at doses of 40 mg/kg/day and above (approximately 22,000 times the maximum recommended daily inhalation dose in adults on a $mg/m^2$ basis). There were no teratogenic findings in rabbits with oral dose of 10 mg/kg and lower (AUC exposure approximately 4900 times adult exposure at the maximum recommended daily inhalation dose).

There are no adequate and well-controlled studies in pregnant women. BROVANA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

## Use in Labor and Delivery

There are no human studies that have investigated the effects of BROVANA on preterm labor or labor at term.

Because beta-agonists may potentially interfere with uterine contractility, BROVANA should be used during labor and delivery only if the potential benefit justifies the potential risk.

### Nursing Mothers

In reproductive studies in rats, arformoterol was excreted in the milk. It is not known whether arformoterol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BROVANA is administered to a nursing woman.

### Pediatric

BROVANA is approved for use in the long term maintenance treatment of bronchoconstriction associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. This disease does not occur in children. The safety and effectiveness of BROVANA in pediatric patients have not been established.

### Geriatric

Of the 873 patients who received BROVANA in two placebo-controlled clinical studies in adults with COPD, 391 (45%) were 65 years of age or older while 96 (11%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Among subjects age 65 years and older, 129 (33%) received BROVANA at the recommended dose of 15 mcg twice daily, while the remainder received higher doses. ECG alerts for ventricular ectopy in patients 65 to $\leq$ 75 years of age were comparable among patients receiving 15 mcg twice daily, 25 mcg twice daily, and placebo (3.9%, 5.2%, and 7.1%, respectively). A higher frequency (12.4%) was observed when BROVANA was dosed at 50 mcg once daily. The clinical significance of this finding is not known. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

## ADVERSE REACTIONS

### Experience in Adult Patients with COPD

Of the 1,456 COPD patients in the two 12-week, placebo-controlled trials, 288 were treated with BROVANA (arformoterol tartrate) inhalation solution 15 mcg twice daily and 293 were treated with placebo. Doses of 25 mcg twice daily and 50 mcg once daily were also evaluated. The numbers and percent of patients who reported adverse events were comparable in the 15 mcg twice daily and placebo groups.

The following table shows adverse events where the frequency was greater than or equal to 2% in the BROVANA 15 mcg twice daily group and where the rates of adverse events in the BROVANA 15 mcg twice daily group exceeded placebo. Ten adverse events demonstrated a dose relationship: asthenia, fever, bronchitis, COPD, headache, vomiting, hyperkalemia, leukocytosis, nervousness, and tremor.

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**Table 1: Number of Patients Experiencing Adverse Events from Two 12 Week, Double-Blind, Placebo Controlled Clinical Trials**

| | BROVANA 15 mcg twice daily | | Placebo | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| Total Patients | 288 | (100) | 293 | (100) |
| Pain | 23 | (8) | 16 | (5) |
| Chest Pain | 19 | (7) | 19 | (6) |
| Back Pain | 16 | (6) | 6 | (2) |
| Diarrhea | 16 | (6) | 13 | (4) |
| Sinusitis | 13 | (5) | 11 | (4) |
| Leg Cramps | 12 | (4) | 6 | (2) |
| Dyspnea | 11 | (4) | 7 | (2) |
| Rash | 11 | (4) | 5 | (2) |
| Flu Syndrome | 10 | (3) | 4 | (1) |
| Peripheral Edema | 8 | (3) | 7 | (2) |
| Lung Disorder* | 7 | (2) | 2 | (1) |

* Reported terms coded to "Lung Disorder" were predominantly pulmonary or chest congestion.

Adverse events occurring in patients treated with BROVANA 15 mcg twice daily with a frequency of <2%, but greater than placebo were as follows:

**Body as a Whole:** abscess, allergic reaction, digitalis intoxication, fever, hernia, injection site pain, neck rigidity, neoplasm, pelvic pain, retroperitoneal hemorrhage

**Cardiovascular**: arteriosclerosis, atrial flutter, AV block, congestive heart failure, heart block, myocardial infarct, QT interval prolonged, supraventricular tachycardia, inverted T-wave

**Digestive:** constipation, gastritis, melena, oral moniliasis, periodontal abscess, rectal hemorrhage

**Metabolic and Nutritional Disorders:** dehydration, edema, glucose tolerance decreased, gout, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia

**Musculoskeletal:** arthralgia, arthritis, bone disorder, rheumatoid arthritis, tendinous contracture

**Nervous:** agitation, cerebral infarct, circumoral paresthesia, hypokinesia, paralysis, somnolence, tremor

**Respiratory:** carcinoma of the lung, respiratory disorder, voice alteration

**Skin and Appendages:** dry skin, herpes simplex, herpes zoster, skin discoloration, skin hypertrophy

**Special Senses:** abnormal vision, glaucoma

**Urogenital:** breast neoplasm, calcium crystalluria, cystitis, glycosuria, hematuria, kidney calculus, nocturia, PSA increase, pyuria, urinary tract disorder, urine abnormality.

Overall, the frequency of all cardiovascular adverse events for BROVANA in the two, placebo controlled trials was low and comparable to placebo (6.9% in BROVANA 15 mcg twice daily and 13.3% in the placebo group). There were no frequently occurring specific cardiovascular adverse events for BROVANA (frequency ≥1% and greater than placebo). The rate of COPD exacerbations was also comparable between the BROVANA 15 mcg twice daily and placebo groups, 12.2% and 15.1%, respectively.

Other adverse reactions which may occur with selective $beta_2$-adrenoceptor agonists such as BROVANA; include angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia.

### Drug Abuse and Dependence

There were no reported cases of abuse or evidence of drug dependence with the use of BROVANA in the clinical trials.

## OVERDOSAGE

The expected signs and symptoms associated with overdosage of BROVANA (arformoterol tartrate) Inhalation Solution are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed under **ADVERSE REACTIONS**, e.g., angina, hypertension or hypotension, tachycardia,

with rates up to 200 bpm, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of BROVANA.

Treatment of overdosage consists of discontinuation of BROVANA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of BROVANA. Cardiac monitoring is recommended in cases of overdosage.

Clinical signs in dogs included flushing of the body surface and facial area, reddening of the ears and gums, tremor, and increased heart rate. A death was reported in dogs after a single oral dose of 5 mg/kg (approximately 4500 times the maximum recommended daily inhalation dose in adults on a $mg/m^2$ basis). Death occurred for a rat that received arformoterol at a single inhalation dose of 1600 mcg/kg (approximately 430 times the maximum recommended daily inhalation dose in adults on a $mg/m^2$ basis).

## DOSAGE AND ADMINISTRATION

The recommended dose of BROVANA (arformoterol tartrate) Inhalation Solution for COPD patients is 15 mcg administered twice a day (morning and evening) by nebulization. A total daily dose greater than 30 mcg (15 mcg twice daily) is not recommended. BROVANA should be administered by the inhaled route via a standard jet nebulizer connected to an air compressor (see the accompanying **Medication Guide).** BROVANA should not be swallowed. BROVANA should be stored refrigerated in individual unit dose, low-density polyethylene (LDPE) vials sealed in single foil pouches. Vials should be removed from the foil pouches and used immediately after opening.

If the recommended maintenance treatment regimen fails to provide the usual response, medical advice should be sought immediately, as this is often a sign of destabilization of COPD. Under these circumstances, the therapeutic regimen should be re-evaluated and additional therapeutic options should be considered.

No dose adjustment is required for patients with renal or hepatic impairment. However, since the clearance of BROVANA is prolonged in patients with hepatic impairment, they should be monitored closely.

The drug compatibility (physical and chemical), efficacy, and safety of BROVANA when mixed with other drugs in a nebulizer have not been established.

The safety and efficacy of BROVANA have been established in clinical trials when administered using the PARI LC PLUS® nebulizers and PARI DURA-NEB® 3000 compressors. The safety and efficacy of BROVANA when administered using other nebulizer systems has not been established.

## HOW SUPPLIED

BROVANA (arformoterol tartrate) Inhalation Solution is supplied in a single strength (15 mcg of arformoterol, equivalent to 22 mcg of arformoterol tartrate) as 2 mL of a sterile solution in unit-dose, low-density polyethylene (LDPE) vials individually overwrapped in foil. BROVANA is available in a shelf-carton containing 30 or 60 individually pouched vials.

NDC 63402-911-30: carton of 30 unit-dose individually pouched vials.

NDC 63402-911-60: carton of 60 unit-dose individually pouched vials.

CAUTION: Federal law (U.S.) prohibits dispensing without prescription.

### Storage

Store BROVANA in the protective foil pouch under refrigeration at 36°-46°F (2°-8°C). Protect from light and excessive heat. Once the foil pouch is opened, the contents of the vial should be used immediately. Discard any vial if the solution is not colorless. Unopened foil pouches of BROVANA can also be stored at room temperature 68°-77°F, (20°-25°C) for up to 6 weeks. If stored at room temperature, discard if not used after 6 weeks or if past the expiration date, whichever is sooner.


Manufactured for:
**Sepracor Inc.**
Marlborough, MA 01752 USA
For customer service, call 1-888-394-7377.
To report adverse events, call 1-877-737-7226.
For medical information, call 1-800-739-0565.

October 2006

Code XXXX

D

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-912

Sepracor Inc.
84 Waterford Drive
Marlborough, MA 01752-7010

Attention: Renee M. Carroll, M.S., RAC
Associate Director, Regulatory Affairs

Dear Ms. Carroll:

Please refer to your new drug application (NDA) dated December 8, 2005, received December 12, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brovana (arformoterol tartrate) Inhalation Solution.

We acknowledge receipt of your submissions dated December 20, 2005, and January 3, and 6, February14, 16, and 22, March 23, 29, and 31, April 11, 18, and 27, May 15, June 7, 15, 16, and 23, July 12, 13, and 21, August 3, 24, 28, and 29, September 6, 12, 19, 20, 27, and 28, and October 2, 4, and 5, 2006.

This new drug application provides for the use of Brovana (arformoterol tartrate) Inhalation Solution for the treatment of bronchoconstriction associated with chronic obstructive pulmonary disease.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, Medication Guide) submitted on October 5, 2006, (immediate container and carton labels) submitted on October 4, 2006. Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-912.**" Approval of this submission by FDA is not required before the labeling is used.

Within 30 days of the date of this letter, submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the labeling text submitted on October 5, 2006. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

We remind you of your postmarketing study commitment(s) in your submission dated October 4, 2006. These commitments are listed below.

1. Conduct a multicenter, randomized, placebo-controlled, large, simple safety trial to evaluate the effects of long term use of BROVANA (arformoterol tartrate) Inhalation Solution in patients with COPD. The objective of this trial is to determine the risk of fatal and life-threatening respiratory events associated with the long term use of BROVANA in patients with COPD. The trial will be of adequate size and duration to meet the objective. The final study report will be submitted as a supplement.

   Protocol Submission Date: August 2007
   Study Start Date: December 2007
   Final Report Submission Date: December 2012

2. Conduct a safety and tolerability study with one or more doses and one or more dose levels of BROVANA (arformoterol tartrate) Inhalation Solution in children with asthma and/or obstructive airway disease. The objective of this study is to assess the safety and tolerability of BROVANA in children 12 years of age and younger with asthma. The study will include a placebo or active control treatment group, as appropriate. The study will also include children age 12 years and younger so that the lower age limit is based upon the age at which asthma/obstructive airway disease exists. The trial will be of adequate size and duration to meet the objective. The final study report will be submitted as a supplement.

   Protocol Submission Date: June 2007
   Study Start Date: September 2007
   Final Report Submission Date: December 2008

3. Conduct a safety and efficacy study with one or more doses and one or more dose levels of BROVANA (arformoterol tartrate) Inhalation Solution in children with asthma and/or obstructive airway disease presenting with an acute exacerbation. The objective of this study is to establish the safety and efficacy of BROVANA in children 12 years of age and younger with an acute exacerbation of asthma. The study will include a placebo or active control treatment group, as appropriate. The study will also include children age 12 years and younger so that the lower age limit is based upon the age at which asthma/obstructive airway disease exists. The trial will be of adequate size and duration to meet the objective. The final study report will be submitted as a supplement.

   Protocol Submission Date: September 2008
   Study Start Date: January 2009
   Final Report Submission Date: May 2011

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled

**"Postmarketing Study Commitment Protocol", "Postmarketing Study Commitment Final Report", or "Postmarketing Study Commitment Correspondence."**

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary and Allergy Products, and two copies of both the promotional materials and the package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

We also remind you of the following Chemistry, Manufacturing, and Controls (CMC) agreements listed in your submission dated September 12, 2006.

1. Submit the validation report for method (b) (4) to the Agency upon completion and prior to commercialization of Brovana Inhalation Solution.

2. Conduct further extractable studies of the foil and submit the data to the NDA.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 301-796-1231.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: PKG Insert, Medguide

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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Badrul Chowdhury
10/6/2006 03:01:19 PM

E

| Terminal Disclaimer To Obviate A Double Patenting Rejection Over A Prior Patent | Docket No. 0701.001F |
|---|---|

In re Application Of:

**ABERG et al.**

| Serial No. | Filing Date | Examiner | Group Art Unit |
|---|---|---|---|
| 09/927,008 | August 9, 2001 | Haghighatian, M. | 1616 |

Invention: **METHODS AND COMPOSITIONS FOR TREATING PULMONARY DISORDERS USING OPTICALLY PURE ( R,R) FORMOTEROL**

Owner of Record: **SEPRACOR, INC.**



TO THE ASSISTANT COMMISSIONER FOR PATENTS:

The above-identified owner of record of a **100** percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior Patent No. **US 5,795,564** . The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors and/or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it later expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of an organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney of record.

Candice J. Clement
*Signature*

Dated: **December 5, 2002**

**Candice J. Clement, Esq.**
*Typed or Printed Name*

12/11/2002 CCHAU1 00000123 09927008
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☒ Terminal disclaimer fee under 37 C.F.R. 1.20(d) included.
☒ PTO suggested wording for terminal disclaimer was unchanged.
☐ Certification under 37 C.F.R. 3.73(b) is required if terminal disclaimer is signed by the assignee.

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**United States Patent and Trademark Office**

| Patent Bibliographic Data | | | | 11/16/2006 11:26 AM | |
|---|---|---|---|---|---|
| **Patent Number:** | 6589508 | | **Application Number:** | 09927008 | |
| **Issue Date:** | 07/08/2003 | | **Filing Date:** | 08/09/2001 | |
| **Title:** | METHODS AND COMPOSITIONS FOR TREATING PULMONARY DISORDERS USING OPTICA | | | | |
| **Status:** | 8th year fee window opens: 07/08/2010 | | | **Entity:** | Large |
| **Window Opens:** | 07/08/2010 | **Surcharge Date:** | 01/11/2011 | **Expiration:** | N/A |
| **Fee Amt Due:** | Window not open | **Surchg Amt Due:** | Window not open | **Total Amt Due:** | Window not open |
| **Fee Code:** | 1552 | MAINTENANCE FEE DUE AT 7.5 YEARS | | | |
| **Surcharge Fee Code:** | | | | | |
| **Most recent events (up to 7):** | 2006/10/30 | Payment of Maintenance Fee, 4th Year, Large Entity.<br>--- End of Maintenance History --- | | | |
| **Address for fee purposes:** | HESLIN ROTHENBERG FARLEY & MESITI P.C.<br>5 COLUMBIA CIRCLE<br>ALBANY, NY<br>12203 | | | | |

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## Selected Activities for BROVANA™ Regulatory Review

| Date | Type | Activity |
|---|---|---|
| **2-20-98** | **IND** | **IND Application (7 volumes)** |
| 2-27-98 | IND | Communication from FDA to Sepracor: Assigned IND# 55,302 for (R,R) –formoterol tartrate. Notated other identifying data for the application. |
| 3-2-98 (A) | IND | Communication from Sepracor to FDA regarding correction to the 2-27-98 letter from the FDA Re: 55,302. |
| 3-2-98 (B) | IND | Communication from Sepracor to FDA regarding request for comparison of 2-98 & 12-97 versions of 091-003 |
| 3-4-98 | IND | Response to 091-003 questions |
| 3-20-98 | IND | Request by FDA for additional one-month and three-month stability data on the drug product |
| 3-23-98 | IND | Submission: IND – stability data for drug product |
| 3-24-98 (A) | IND | Submission: IND – stability data for drug product |
| 3-24-98 (B) | IND | Communication from Sepracor to FDA regarding container closure system |
| 3-25-98 | IND | Communication from Sepracor to FDA regarding 20 mL bottle data-White Colorant information |
| 3-26-98 (A) | IND | Request by FDA regarding pigment |
| 3-26-98 (B) | IND | Communication from Sepracor to FDA regarding initiation of Clinical Program |
| 3-27-98 | IND | Communication from Sepracor to FDA regarding white colorant information |
| 4-2-98 | IND | Communication from Sepracor to FDA regarding white Colorant information |
| 4-3-98 | IND | Teleconference between Sepracor and FDA regarding white pigments |
| 4-13-98 | IND | Submission: Faxed Container-Closures Data (1 volume) |
| 5-6-98 | IND | Submission: Protocol 003 & Final Investigator Brochure (1 volume) |
| 6-22-98 | IND | Communication from FDA to Sepracor providing comments from review of IND |
| 9-18-98 | IND | Protocol Amendment: Change in Protocol 091-003, New Investigators (1 volume) |
| 9-28-98 | IND | Response to FDA request for information; Information Amendment: Pharmacology- Toxicology (3 Genotoxicity reports, 1 volume) |
| 12-8-98 | IND | Submission: 2 Clinical reports (091-001, 091-002, 2 volumes) |
| 3-11-99 | IND | Submission: Initial IND safety report for Study 091-003 describing results of a teratology study in rabbits (preclinical embryo/fetal development) |
| 5-20-99 | IND | Submission: Annual Report covering the period from 26 March 1998 to 25 March 1999 |
| 7-23-99 | IND | Information Amendment: Pharm/Tox<br>Request for Review of Dose Selection Rationale for the Proposed 2-Year Inhalation Carcinogenicity Study in Rats (1 volume) |
| 8-4-99 | IND | Request by FDA for full audited draft report for the 28-Day Inhalation Toxicity Study in Rats |
| 8-11-99 | IND | Information Amendment: Pharm/Tox [new protocol for Study WIL-312050 (6-month inhalation study in rats) and final report for Study WIL-312021] |
| 8-17-99 | IND | Information Amendment: Pharm/Tox (final Tox and TK reports for Study WIL-312022, a 28-day inhalation study in dogs) |

| Date | Type | Activity |
|---|---|---|
| 9-17-99 | IND | Communication from FDA to Sepracor providing minutes of 9-7-99 Committee meeting with recommendations for the proposed rat study |
| 12-13-99 | IND | Protocol Amendment: New Protocol<br>New Protocol 091-004 and updated Investigator's Brochure dated December 1999 |
| 12-14-99 | IND | Information Amendment: CMC (Drug substance section includes information on establishement of absolute stereochemistry of the molecule and current method of manufacturing and controls processes. Drug product section provides CMC for two new doses: 0.096 mg/mL and 0.144 mg/mL.) |
| 1-21-2000 | IND | Communication from FDA to Sepracor providing comments regarding amendments dated September 28, 1998, and August 11 and 17, 1999 (serial numbers 005, 010, and 011), containing genetic and general toxicology reports of 4-week duration in rats and dogs, and a proposal for a 6-month inhalation toxicity study in rats |
| 2-4-2000 | IND | Information Amendment: Pharm/Tox (five pre-clinical reports: 090-460, 090-813, 090-464, 090-809, and 090-814) |
| 2-15-2000 | IND | Protocol Amendment: New Investigators (sixteen new investigators for Protocol 091-004) |
| 3-9-2000 | IND | Response to FDA Request for Information (preclinical information and data requested in FDA letter of January 21, 2000) |
| 3-15-2000 | IND | Protocol Amendment: Change in Protocol, New Investigator (Amendment 1 and Revised Protocol 1 for study 091-004 and nineteen new investigators for study 091-004) |
| 4-14-2000 | IND | Protocol Amendment: New Investigator (six investigators for Protocol 091-004) |
| 5-19-2000 | IND | Protocol Amendment: New Investigator (three new investigators for Protocol 091-004) |
| 5-24-2000 | IND | Submission: Annual Report for period of March 26, 1999, to March 31, 2000 |
| 6-6-2000 | IND | Protocol Amendment: New Investigator - Revised 1572 Forms (10 sites) |
| 6-7-2000 | IND | Protocol Amendment: New Investigator |
| 6-27-2000 | IND | Protocol Amendment: New Investigator - Revised 1572 Forms for 091-004 (3 sites) |
| 9-5-2000 | IND | Protocol Amendment: New Investigator - Revised 1572 Forms (change in lab name from UCT International to ICON Laboratories for Protocol 091-004) |
| 10-10-2000 | IND | Protocol Amendment: New Protocol, New Investigator (Protocol 091-021) |
| 11-6-2000 (A) | IND | Protocol Amendment: New Investigators Add 3 new PIs to Protocol 091-021 |
| 11-6-2000 (B) | IND | Protocol Amendment: New Investigator - Revised 1572 Forms for 3 PIs for Protocol 091-004 |
| 12-6-2000 | IND | Protocol Amendment: New Investigator – Add 2 new PIs for Protocol 091-021, revised 1572 Form |
| 2-1-2001 | IND | Protocol Amendment: New Investigator for 091-021 and Information Amendment: Pharmacology/ Toxicology (10 preclinical reports and 1 amendment to a final report) (two volumes) |
| 3-16-2001 | IND | Protocol Amendment: New Investigator Information Amendment: Pharmacology/ Toxicology (Revised 1572s for Drs. Corren and Corser for Protocol 091-021, plus 11 new preclinical reports) (10 volumes) |

| Date | Type | Activity |
|---|---|---|
| 5-4-2001 | IND | Protocol Amendment: Change in Protocol (Amendment 2 for 091-021) and Information Amendment: Pharmacology/Toxicology (one protein binding report and five new bioanalytical reports) |
| 5-10-2001 | IND | Request by FDA for the list of Sepracor attendees for the 5-11-01 teleconference. |
| 5-14-2001 (A) | IND | Faxed requested list of Sepracor attendees for May 11, 2001 teleconference. |
| 5-14-2001 (B) | IND | Request by FDA for another teleconference for May 15 or 16, 2001, to discuss Protocol 091-021 |
| 5-15-2001 | IND | Information Amendment: CMC (new formulations of 0.015 mg/mL, 0.030 mg/mL, and 0.060 mg/mL, each in 1 mL unit-dose vials) |
| 5-16-2001 | IND | Communication from Sepracor to FDA briefing documents for teleconference scheduled for May 16, 2001 for the discussion of Protocol 091-021 |
| 5-24-2001 (A) | IND | Communication from Sepracor to FDA regarding revised timeline for providing information requested during May 16, 2001, teleconference. |
| 5-24-2001 (B) | IND | Communication from FDA to Sepracor confirming receipt of revised information timeline |
| 5-24-2001 (C) | IND | Request by FDA for a teleconference on June 4, 2001, regarding a general discussion of adverse event reporting during clinical studies |
| 5-25-2001 (A) | IND | General Correspondence: Requested List of Submissions. Protocol 190-001 – 190-004. |
| 5-25-2001 (B) | IND | Communication from Sepracor to FDA regarding copy of Submission Serial No. 034 sent to Robert Meyer |
| 6-1-2001 | IND | Communication from Sepracor to FDA requesting information on the timing of teleconference to discuss Adverse Event Reporting would be held. |
| 6-5-2001 (A) | IND | Request by FDA for attendees' names for teleconference held June 4, 2001, regarding safety reporting |
| 6-5-2001 (B) | IND | Submission: Notice to Division that Serial No. 033 was inadvertendly omitted from reporting sequence |
| 6-5-2001 (C) | IND | Communication from Sepracor to FDA providing copy of cover letter and Form FDA 1571 for Serial No. 035 |
| 6-5-2001 (D) | IND | General Correspondence: Withdrawal of Protocol Amendment (Amendment 2 to Protocol 091-021 submitted May 4, 2001, in Serial No. 031) |
| 6-6-2001 (A) | IND | Submission: IND Annual Report (April 1, 2000 through March 31, 2001) |
| 6-6-2001 (B) | IND | Submission: Proposal for Juvenile Nonclinical Safety Assessment of (R,R)-Formoterol |
| 6-12-2001 | IND | Information Amendment: Pharmacology/Toxicology, Report #'s 090-818, 090-534, 090-536. |
| 6-22-2001 | IND | Communication from Sepracor to FDA regarding request for an EOP2 Meeting |
| 6-28-2001 | IND | Submission: Initial IND Safety Reports , 091-021 for subjects: JT/S023/R0054, SAT/S007/R0107, TCT/S021/R0113, LMK/S004/R0024 |

| Date | Type | Activity |
|---|---|---|
| 7-3-2001 (A) | IND | Communication from Sepracor to FDA faxing a copy of Serial No. 040 |
| 7-3-2001 (B) | IND | General Correspondence: End of Phase 2 Meeting Report |
| 7-16-2001 | IND | Information Amendment: Pharmacology/Toxicology, Report #'s 090-417, -418, -419, -452, & -475 |
| 7-17-2001 | IND | FDA proposals for End of Phase II meeting |
| 8-7-2001 (A) | IND | Fax from Sepracor to FDA forwarding the End of Phase II Meeting Information Package |
| 8-7-2001 (B) | IND | Submission: End of Phase II Meeting Information Package |
| 8-7-2001 (C) | IND | Communication between Sepracor and FDA regarding eeting for EOPII set for 9/6/2001 |
| 8-29-2001 (A) | IND | Communication from Sepracor to FDA informing the realignment of projects along Therapeutic Areas, and regarding the EOP II meeting |
| 8-29-2001 (B) | IND | Protocol Amendment, New Protocol 091-010, and new investigator for 091-010 |
| 8-29-2001 (C) | IND | Communication from FDA to Sepracor regarding the time slot for CMC section of the EOPII meeting |
| 8-29-2001 (D) | IND | Communication from FDA to Sepracor providing the list of attendees for September 6, 2001 EOP II Meeting |
| 8-30-2001 | IND | Communication from FDA to Sepracor finalizing EPO II meeting time and place |
| 8-31-2001 | IND | Communication from Sepracor to FDA regarding EOP II Meeting preparation |
| 9-12-2001 | IND | Submission: Revised Initial IND Safety Report for subject TCT/S021/R0113. |
| 9-18-2001 | IND | General Correspondence: Follow up to the End of Phase 2 meeting, EOP2 Draft Minutes, Request for a Teleconference. |
| 9-20-2001 | IND | Communication from Sepracor to FDA reporting on status of submissions |
| 10-1-2001 | IND | Information Amendment: Pharmacology/Toxicology |
| 10-4-2001 | IND | Communication from Sepracor to FDA regarding transfer of Regulatory Responsibility, Project Updates |
| 10-10-2001 | IND | Communication from Sepracor to FDA providing project update |
| 10-11-2001 | IND | General Correspondence: End of Phase 2 Meeting Minutes (CMC) |
| 10-12-2001 | IND | Project update |
| 10-22-2001 | IND | Protocol Amendment: Protocol 091-010 New Investigators, Revised Form FDA 1572 |
| 10-23-2001 (A) | IND | Submission: IND Safety Report: Initial Report (Subject TRW/S001), Initial Report (Subject LJO/S006) |
| 10-23-2001 (B) | IND | Communication from Sepracor to FDA providing project update |
| 10-25-2001 | IND | Communication from Sepracor to FDA providing comments on Protocol 091-050 |

| Date | Type | Activity |
|---|---|---|
| 11-1-2001 | IND | Communication from Sepracor to FDA regarding protocol 091-050 and 091-051 and the progress of each |
| 11-2-2001 | IND | Submission: Request for Special Protocol Assessment: Protocol 09-051 |
| 11-6-2001 | IND | Communication from FDA to Sepracor requesting an additional copy of Serial No. 050 |
| 11-7-2001 (A) | IND | General Correspondence: Additional Copy of Serial No. 050 |
| 11-7-2001 (B) | IND | Communication from Sepracor to FDA regarding the additional copy of 091-051, the Division's Minutes from the EOP2 Meeting and the status of proposal for Juvenile Nonclinical Risk Assessment submitted on 6-6-01 |
| 11-20-2001 | IND | Communication from Sepracor to FDA regarding minutes from EOP2 meeting held in September and feedback on proposal for Juvenile Nonclinical Risk Assessment |
| 11-27-2001 | IND | Communication from Sepracor to FDA regarding questions concerining Protocols 091-050 and 091-051 |
| 11-30-2001 | IND | Communication from Sepracor to FDA regarding the submission of Protocol 091-050 on 11/7/01 in Serial No 051; the EOP2 Meeting Minutes; Clinical Studies for 091-003 and 091-004; and the 9-month dog study |
| 12-3-2001 | IND | FDA Request for Additional Copy of Serial No. 050 |
| 12-4-2001 | IND | General Correspondence: Additional Copy of Serial No. 050 |
| 12-14-2001 | IND | Communication between Sepracor and FDA regarding the status report for the special protocol assessment (091-051) and the 8 volume Nonclinical IND Information to be submitted |
| 12-17-2001 | IND | FDA acknowledgement of receipt of serial no. 050 |
| 12-18-2001 | IND | Information Amendment: Pharmacology/Toxicology |
| 12-19-2001 | IND | Request by Sepracor for a status update on Special Protocol Assessment for study 091-051 |
| 12-20-2001 (A) | IND | Communication from FDA to Sepracor providing a letter containing FDA responses to questions regarding study 091-051 |
| 12-20-2001 (B) | IND | FDA responses to questions regarding study 091-051. |
| 1-4-2002 | IND | Information Amendment: Chemistry, Manufacturing, and Controls |
| 1-14-2002 | IND | Communication between Sepracor and FDA regarding the status report concerning the Division's minutes from the 9/6/01 EOP2 meeting. |
| 2-7-2002 | IND | Protocol Amendment: New Protocol, New Investigator (Protocol 091-050, V.1.2 dated 1-9-02, Amendment 2 dated 1-7-02, Amendment 1 dated 11-13-01) |
| 2-15-2002 | IND | Information Amendment: Pharmacology/ Toxicology (Sepr. Doc. Nos. 090-483, 090-489, 090-550, and 090-532) |
| 2-27-2002 | IND | Request by Sepracor for information regarding the date for receipt of the Division's minutes of the 9-6-01 EOP2 meeting |
| 2-28-2002 (A) | IND | Protocol Amendment: New Investigators<br>(21 investigators for 091-050) |
| 2-28-2002 (B) | IND | Request by FDA for clarification on changes made to Protocol 091-050 (Serial No. 054); answer provided by Sepracor |

| Date | Type | Activity |
|---|---|---|
| 3-15-2002 | IND | Response to FDA Request for Information (Protocol 091-050 highlighted and with track changes) |
| 3-28-2002 | IND | Protocol Amendment: New Investigators (13) protocol 091-050 |
| 4-12-2002 | IND | Protocol Amendment: New Protocol, New Investigator (091-051) |
| 4-25-2002 | IND | Information Amendment: Pharmacology/Toxicology |
| 4-30-2002 | IND | Protocol Amendment: New Investigators (8) Study 091-050 |
| 5-8-2002 | IND | Submission: IND Safety Report: Initial Report (Subject BLA/S007/R0024) 091-050 |
| 5-13-2002 | IND | Protocol Amendment: New Investigators (12) Study 091-051 |
| 5-16-2002 | IND | Communication between Sepracor and FDA regarding the status of the Formoterol EOP II minutes from the September 6, 2001 meeting |
| 5-21-2002 | IND | Communication between Sepracor and FDA regarding the status of the Formoterol EOP II minutes from the September 6, 2001 meeting |
| 5-22-2002 | IND | Protocol Amendment: New Protocol, New Investigator (091-014) and New Protocol, New Investigator (091-015) |
| 6-3-2002 (A) | IND | Protocol Amendment: New Investigators (091-014, 091-050 and 091-051) |
| 6-3-2002 (B) | IND | Communication between Sepracor and FDA regarding Sepracor's request for a copy of the slides from the EOP-II CMC Meeting. |
| 6-3-2002 (C) | IND | Communication between Sepracor and FDA regarding the EPOII Meeting Minutes from the Division |
| 6-4-2002 (A) | IND | Communication from Sepracor to FDA regarding change in corporate address |
| 6-4-2002 (B) | IND | Fax from FDA of the slides from the EOP-II CMC Meeting. |
| 6-5-2002 (A) | IND | Protocol Amendment: New Protocol, New Investigator (091-060) |
| 6-5-2002 (B) | IND | Adverse Event Report: IND Safety Report Initial: S009/R0061/DLH |
| 6-18-2002 (A) | IND | Submission: IND Annual Report (April 1, 2001 through March 31, 2002) |
| 6-18-2002 (B) | IND | Communication between Sepracor and FDA regarding the status of the EPOII Meeting Minutes |
| 6-19-2002 | IND | Request by FDA for an electronic copy of the slides presented at the EOPII Meeting |
| 6-20-2002 | IND | IND Safety Report: Initial Report (Subject BLA/S007/R0024) |
| 6-25-2002 | IND | Communication from FDA to Sepracor providing comments from FDA on Serial No. 064, dated May 22, 2002 Protocol NO. 091-014 |
| 7-1-2002 (A) | IND | Submission: IND Safety Report: Follow-up Report (Subject S007/R0024/BLA) 091-050 |

| Date | Type | Activity |
|---|---|---|
| 7-1-2002 (B) | IND | Communication between Sepracor and FDA regarding the CMC portion of the EOPII Meeting Minutes from the 9/6/01 meeting |
| 7-3-2002 | IND | FDA Official Minutes from September 6, 2001, EOPII CMC Meeting |
| 7-8-2002 | IND | Protocol Amendment: New Investigators |
| 7-9-2002 | IND | Submission: IND Safety Reports: Initial Report (Subject S008/R0840/RHS) Initial Report (Subject S014/R0869/JMW) Study 091-050 |
| 7-12-2002 (A) | IND | Submission: IND Safety Reports: Initial Report (S004/R0209/CAA) and Initial Report (S014/R0869/JMW) studies 091-050/091-020 |
| 7-12-2002 (B) | IND | Communication from Sepracor to FDA providing an electronic copy of Sepracor's Slides presented at the 9-6-01 EOP2 Meeting |
| 7-19-2002 | IND | Official FDA Minutes for EOPII (non-CMC) 9-6-01 Meeting |
| 7-23-2002 | IND | Submission: IND Safety Reports: Initial Reports: Subject Nos. S001/0818/HRS, S017/R0088/PEY, S034/R0868/MAH and Follow-up Reports: Subject Nos. S008/R0840/RHS and S014/R0869/JMW. Study # 190-050 |
| 7-26-2002 | IND | Submission: IND Safety Reports: Initial Reports (S015/R0191/KDG and S047/R0225/LAT) and Follow-up Report (S034/R0868/MAH) study 091-050 |
| 7-31-2002 | IND | Submission: IND Safety Reports: Initial Reports (Subject S008/R0205/PMS and S001/R5004/EMW) study 091-051 |
| 8-1-2002 | IND | Protocol Amendment: Revised Protocol (091-014 and 091-015) |
| 8-8-2002 | IND | Protocol Amendment: New Investigators (3-050, 6-051 and 18-060) |
| 8-9-2002 | IND | Submission: IND Safety Reports: Initial Report (Subject S013/R0176/GAP) Follow-up Report (Subject S001/R5004/EMW) studies 091-050/091-051 |
| 8-12-2002 | IND | Submission: IND Safety Reports: Initial Report (Subject S019/R0849/DMB and Initial Report (Subject S043/R0885/KMS) study 091-050 |
| 8-15-2002 (A) | IND | Request by FDA for Missing Page 2, Form FDA 1572 for Dr. V. Patel, from Serial No. 079, dated 8-9-2002. |
| 8-15-2002 (B) | IND | General Correspondence: Response to Request for Information, Provide Missing Page 2, Form FDA 1572 for Dr. V. Patel |
| 8-16-2002 | IND | Submission: IND Safety Reports: Follow-up Report (Subject S001/R0818/HRS) and Follow-up Report (Subject S001/R5004/EMW) study 091-050/091-051 |
| 8-21-2002 | IND | Submission: IND Safety Report: Follow Up Report (Subject S014/R0869/JMW) |
| 8-27-2002 | IND | Communication between Sepracor and FDA regarding the timeline for submission of a marketing application |
| 9-3-2002 | IND | Submission: IND Safety Report: Initital Report (Subject S007/R0919/SEY) study 091-050 |
| 9-10-2002 | IND | Communication between Sepracor and FDA regarding Investigator Dr. W. Busse |
| 9-11-2002 | IND | Protocol Amendment: New Investigators (-050, -051, -060) |
| 9-13-2002 | IND | Protocol Amendment: New Protocol, New Investigator (091-013) |
| 9-16-2002 | IND | Submission: IND Safety Reports: Initial Report (Subject S014/R0923/DCR study –050) Follow up (Subject S007/R0919/SEY study –050) Follow up (Subject S008/R0205/PMS study –014) |

| Date | Type | Activity |
|---|---|---|
| 9-17-2002 | IND | Submission: IND Safety Report: Initial Report (Subject S007/R0051/PRC) study 091-050 |
| 9-20-2002 | IND | Submission: IND Safety Reports: Initial Report (Subject S916/R2073/RAM) 091-060, Initial Report (Subject S018/R0122/HTH) 091-050, Initial Report (Subject S013/R0299/J-R) 091-050, Follow-up Report (Subject S013/R0176/GAP) 91-050 and Follow-up Report (Subject S009/R0061/DLH) 091-050 |
| 9-26-2002 | IND | Submission: IND Safety Reports: Initial Reports (Subject S906/R2121/MWM) 3 initial reports on same subject for study 091-060 |
| 9-27-2002 (A) | IND | Information Amendment: Pharmacology / Toxicology |
| 9-27-2002 (B) | IND | Submission: IND Safety Reports: Initial Report (Subject S028/R0905/ZAF) Initial Report (Subject S045/R0895/JEC) Follow-up (Subject S014/R0923/DCR) Follow-up (Subject S015/R0191/KDG) Study 091-050 |
| 10-1-2002 | IND | Submission: IND Safety Reports: Follow-up Report (Subject S014/R0869/JMW 091-050) and Follow-up Report (Subject S018/R0122/HTH 091-050) |
| 10-2-2002 | IND | Telephone discussion between Sepracor and FDA regarding FDA's comments on protocol 091-013 submitted on 9/19 |
| 10-7-2002 | IND | Submission: IND Safety Report: Follow-up Report (Subject S034/R0868/MAH) 091-050 |
| 10-9-2002 | IND | Protocol Amendment: New Investigators (-015, -050, -051, -060) Revised 1572's (-014, -015, -050, -051) |
| 10-11-2002 | IND | Submission: IND Safety Reports: Follow Up Reports (Subject S043/R0885/KMS [091-050], Subject S028/R0905/ZAF [091-050], Subject S906/R2121/MWM [091-060], Subject S916/R2073/RAM [091-060]) |
| 10-15-2002 | IND | Submission: IND Safety Reports: Follow Up Reports (Subject S007/R0051/PRC [091-050], Subject S045/R0895/JEC [091-050], Subject S906/R2121/MWM [091-060]) |
| 10-16-2002 | IND | Communication from FDA to Sepracor providing preliminary Clinical Pharmacology comments on protocol 091-013 |
| 10-24-2002 | IND | Submission: IND Safety Report: Follow Up Report (Subject S034/R0868/MAH [091-050]) |
| 10-31-2002 | IND | Submission: IND Safety Report: Follow Up Report (Subject S015/R0191/KDG [091-050]) |
| 11-1-2002 | IND | Submission: IND Safety Report: Follow up report (Subject S007/R0919/SEY) study 091-050 |
| 11-5-2002 (A) | IND | Protocol Amendment: New Protocol, New Investigator [091-012] |
| 11-5-2002 (B) | IND | Submission: IND Safety Report: Follow Up Report (Subject S013/R0299/J-R [091-050]) |
| 11-7-2002 | IND | Submission: IND Safety Report: Initial Reports (Subject S0905/R2125/QBM [091-060], Subject S506/R2020/GPS [091-060], Subject S001/R5086/BJN [091-051], Subject S015/R0925/DAR [091-050), Follow Up Report (Subject S047/R0225/LAT [091-050]) |
| 11-8-2002 | IND | Information Amendment: CMC |
| 11-11-2002 (A) | IND | Protocol Amendment: New Investigators (3) 091-051, (9) 091-060 |
| 11-11-2002 (B) | IND | Information Amendment: CMC<br>Protocol Amendment: New Protocol, New Investigator (091-016) |

| Date | Type | Activity |
|---|---|---|
| 11-11-2002 (C) | IND | Submission: IND Safety Reports: 2 Initial Reports for Study 091-051 (Subject S010/R5151/FAE, Subject S007/R5810/J-W) |
| 11-11-2002 (D) | IND | Communication from Sepracor to FDA providing a fax copy of IND Initial Safety Report (7-Day) |
| 11-12-2002 | IND | Submission: Hard copy of IND Safety Report: 7-Day Fax Transmission (Subject S020/R5089/DLO) |
| 11-14-2002 (A) | IND | Submission: IND Safety Report: Initial Report (Subject S014/R0923/DCR) Follow-up Report (Subject S007/R5810/J-W) study 091-050/091-051 |
| 11-14-2002 (B) | IND | Communication from FDA to Sepracor providing Confidentiality Certificate protecting the identity of research subjects involved in clinical studies under IND 55,302 |
| 11-15-2002 | IND | Submission: IND Safety Reports: Initial Report (Subject S012/R5093/CJW [091-051]) and Follow Up Report (Subject S013/R0299/J-R [091-050]) |
| 11-26-2002 | IND | Submission: IND Safety Reports: Initial Report (Subject S005/R5114/WCG) Follow-up Report (Subject S012/R5093/CJW) |
| 11-27-2002 (A) | IND | Communication from Sepracor to FDA providing a fax copy of IND Safety Report Initial Report (7 day fax transmission) Follow-up Report (7 day fax transmission) |
| 11-27-2002 (B) | IND | Submission: Hard copy of IND Safety Reports faxed on this date. (Subject S025/R5177/NGB, Subject S007/R5810/J-W) |
| 12-2-2002 (A) | IND | Submission: IND Safety Reports: Study 091-050 Initial & Follow-up (S004/R0399/WAD, S018/R0122/HTH), Study 091-051 - 1 Initial, 2 follow-up (S007/R5154/JKH, S010/R5151/FAE, S020/R5089/DLO) |
| 12-2-2002 (B) | IND | Information Amendment: CMC |
| 12-6-2002 (A) | IND | Protocol Amendment: New Investigators (7) 1 –016, 1-051, 5-060 |
| 12-6-2002 (B) | IND | Submission: IND Safety Report: Follow-up Report: Subject S025/R5177/NGB, study 091-051 |
| 12-6-2002 (C) | IND | IND Safety Report: 7-Day Fax Transmission, study 091-051 |
| 12-9-2002 | IND | Submission: Hard copy of IND Safety Report: 7-Day Fax Transmission, study 091-051 originally sent on 12/6/2002 |
| 12-10-2002 | IND | Submission: IND Safety Reports: Initial Report (Subject S004/R5125/DLB [091-051]), Follow Up Report (Subject S017/R0088/PEY [091-050]) |
| 12-12-2002 | IND | Telephone discussion between Sepracor and FDA regarding Clinical Pharmacology questions on study 091-016 |
| 12-13-2002 | IND | Submission: IND Safety Report: Initial Report (Subject S015/R0942/JMB [091-050]) |
| 12-16-2002 | IND | Submission: IND Safety Reports: Follow up Report (Subject S004/R0399/WAD study –050) Follow up Report (Subject S005/R5114/WCG study –051) |
| 12-17-2002 | IND | Submission: IND Safety Reports: Initial Report (Subject 903/R2123/LJM study 091-060) Initial Report (Subject S919/R20075/H-S study 091-060) Follow up Report (Subject S906/R2121/MWM study 091-060) |

| Date | Type | Activity |
|---|---|---|
| 12-20-2002 (A) | IND | Protocol Amendment: Revised Protocols –050, -051 and -060 |
| 12-20-2002 (B) | IND | Submission: IND Safety Reports: 3 Initial and 6 Follow –up Subject S010/R0317/FMF, Subject S906/R2121/MWM, Subject S009/R0140/DLS, Subject S906/R2121/MWM, Subject S009/R0240/DLS, Subject S919/R2075/H-S, Subject S018/R0122/HTH, Subject S004/R5125/DLB, Subject S002/R5073/EHW |
| 12-23-2002 | IND | Submission: IND Safety Report: Follow Up Report (Subject S903/R2123/LJM [091-060]) |
| 1-2-2003 (A) | IND | Submission: IND Safety Report: Initial Report (Subject S502/R2189/KMC [091-060]), (2) Follow Up Report (Subject S015/R0942/JMB [091-050]) |
| 1-2-2003 (B) | IND | Communication from FDA to Sepracor regarding comments on the 091-016 protocol from the biopharmaceutics reviewer |
| 1-2-2003 (C) | IND | Communication from FDA to Sepracor providing comments pertaining to Protocol 091-016 |
| 1-3-2003 | IND | Submission: IND Safety Reports: Follow Up Report (Subject S010/R0317/FMF [-050]), Follow Up Report (Subject S906/R2121/MWM [-060]), Follow Up Report (Subject S005/R5114/WCG [-051]) |
| 1-6-2003 | IND | Submission: IND Safety Reports: Initial Report (Subject S503/R220/ERB [091-060]), Initial Report (Subject S005/R5114/WCG [091-051]) |
| 1-8-2003 | IND | Protocol Amendment: New Investigators (091-051 [1], 091-060 [2]) |
| 1-10-2003 | IND | Submission: IND Safety Reports: Initial Report (Subject S013/R0385/BAP, Initial Report (Subject S022/R0349/NSD, Initial Report (Subect S059/R0438/TRW) [-050]; Initial Report (Subject S919/R2075/H-S), Initial Report (Subject S503/R2240/RGB) [-060]; Follow Up Report (Subject S010/R5151/FAE) [-051] |
| 1-13-2003 | IND | Submission: IND Safety Reports 2 Initial Reports (Subject S012/R5242/PJS and Subject S501/R2139/LWP) studies –051 and -060 |
| 1-15-2003 | IND | Submission: IND Safety Reports 1 Initial Report (Subject S919/R2075/H-S) 2 Follow up Reports (Subject S919/R2075/H-S) (Subject S059/R0438/TRW) studies –050 and -060 |
| 1-17-2003 | IND | Submission: IND Safety Report 1 Follow-up Report (Subject S009/R0240/DLS) study–050 |
| 1-21-2003 (A) | IND | Submission: IND Safety Reports: 4 Follow-up Reports for the same subject (S906/R121/MWM) |
| 1-21-2003 (B) | IND | Submission: IND Safety Report: Follow-up report (Subject S0502/R2189/KMC) |
| 1-22-2003 (A) | IND | Submission: IND Safety Reports: 2 initial/1 follow-up Studies –050 and –060 (Subjects S904/R2217/JLL, S049/R0428/L-F, S013/R0385/BAP) |
| 1-22-2003 (B) | IND | Submission: IND Safety Report: Follow-up Report (Subject S014/R0923/DCR) study -050 |
| 1-23-2003 | IND | Submission: IND Safety Reports: 3 Initial Reports studies –050 and –060 (Subject S047/R0397/BJD, S503/R2200/ERB, S525/R2104/EFA) |
| 1-24-2003 | IND | Submission: IND Safety Report: Follow-up Report (Subject S004/R0399/WAD) study 091-050 |
| 1-28-2003 | IND | Submission: IND Safety Reports: 3 Initial, 2 Follow-up (Subjects S042/R0410/JEF, S512/R2245/CHL, S502/R2189/KMC, S022/R0349/NSD, S503/R2240/RGB) Studies –050 and -060 |

| Date | Type | Activity |
|---|---|---|
| 1-29-2003 | IND | Submission: IND Safety Report: 3 Follow-up reports (Subject S007/R5810/J-W, Subject S002/R5073/EHW, Subject S025/R5177/NGB [091-051]) |
| 2-3-2003 | IND | Submission: Initial IND Safety Report: (7-Day Fax Transmission) Study 091-060, (Subject No. S503/R2009/MHK) |
| 2-4-2003 | IND | Submission: IND Safety Reports: Copy of 7-Day Fax Transmission (Subject S503/R2009/MHK [091-060]), Follow up Report (Subject S015/R0925/DAR [091-050]) |
| 2-6-2003 | IND | Submission: IND Safety Reports: 1 Initial (Subject S026/R5229/SEP) 3 Follow-up (Subject S025/R5177/NGB, S018/R0122/HTH, S503/R2200/ERB) Studies –050, -051, -060 |
| 2-7-2003 | IND | Submission: IND Safety Reports: 1 Initial (Subject S028/R0419/HGS) 7 Follow-up (Subjects S047/R0397/BJD, S022/R0349/NSD, S001/R5086/BJN, S905/R2125/QBM, S004/R0399/WAD and 2 for S919/R2075/H-S) studies –050, -051 and -060 |
| 2-10-2003 (A) | IND | Protocol Amendment: Revised Protocol (091-016) |
| 2-10-2003 (B) | IND | Protocol Amendment: New Investigators (091-060) |
| 2-11-2003 | IND | Submission: IND Safety Report: Follow-up Report (Subject S026/R5229/SEP) study 091-051 |
| 2-13-2003 | IND | Submission: IND Safety Reports: Initial Report (Subject S502/R2004/RDH [091-060]), Follow up Report (Subject S503/R2200/ERB [091-060]) |
| 2-14-2003 | IND | Submission: IND Information Amendment: Pharmacology / Toxicology. 7 nonclinical studies |
| 2-20-2003 | IND | Submission: IND Safety Reports: Follow Up Report (Subject S509/R0438/TRW [-050]), Follow Up Report (Subject S007/R5810/J-W [-051]) |
| 2-21-2003 | IND | Submission: IND Safety Report: Follow-up Report: (Subject S508/R2009/MHK) study -060 |
| 2-28-2003 (A) | IND | Communication from Sepracor to FDA providing IND Safety Report (7-Day Fax Transmission) Subject No. S010/R0317/FMF study 091-050 |
| 2-28-2003 (B) | IND | Submission: IND Safety Reports: 6 Initial, 2 Follow-up (Subject No. S007/R0950/RAL [2 initial reports])(Subject No. S065/R0436/EAM) (Subject No. S049/R0428/L-F) (Subject No. S902/R2273/JCK) (Subject No. S501/R2028/RDW) (Subject No. S502/R2189/KMC) (Subject No. S010/R0317/FMF) Studies –050 and -060 |
| 2-28-2003 (C) | IND | Communication from Sepracor to FDA regarding assignment changes in regulatory directors at Sepracor |
| 3-4-2003 | IND | Submission: IND Safety Reports: Follow Up Report (Subject S503/R2009/MHK), Follow Up Report (Subject S501/R2028/RDW) study 091-060 |
| 3-7-2003 | IND | Protocol Amendment: New Investigators (091-051, 091-060) |
| 3-10-2003 | IND | Submission: IND Safety Report: Follow-up report (Subject S026/R5529/SEP) study 091-051 |
| 3-12-2003 | IND | Submission: IND Safety Reports: Initial Report (Subject S510/R2050/ADC) Initial Report (Subject S063/R0968/MAO) Follow-up Report (Subject S049/R0428/L-F) Studies –050 and -060 |
| 3-17-2003 | IND | Telephone discussion between Sepracor and FDA regarding SAE Reporting Schedules |
| 3-18-2003 | IND | Protocol Amendment: Revised Protocol (091-012) |
| 3-20-2003 | IND | Submission: IND Safety Reports: 1 initial (Subject S024/R0970/MJW) and 1 follow-up (Subject S010/R0317/FMF) study -050 |

| Date | Type | Activity |
|---|---|---|
| 3-21-2003 | IND | Submission: IND Safety Reports: 1 Initial Report (Subject S001/R5299/WCM [-051]), 3 Follow Up Reports (Subject S025/R5177/NGB [-051]), (Subject S007/R0950/RAL [-050]), (Subject S902/R2273/JCK [-060]) |
| 3-24-2003 | IND | Submission: IND Safety Reports: Follow Up Report (Subject S028/R0419/HGS [091-050]), Follow Up Report (Subject S024/R0970/MJW [091-050]) |
| 3-31-2003 | IND | Telephone discussion between Sepracor and FDA regarding the Unblinded SAEs from the Program Safety Evaluation |
| 4-1-2003 (A) | IND | Submission: IND Safety Reports: Initial Report (Subject S504/R2281/DHK [-060]) Follow Up Report (Subject S501/R2028/RDW [-060]), Follow Up Report (Subject S510/R2050/ADC [-060]), Follow Up Report (Subject S026/R5229/SEP [-051]) |
| 4-1-2003 (B) | IND | Protocol Amendment: New Investigators (091-051, 091-060) |
| 4-2-2003 | IND | Submission: IND Safety Report: Initial Report (Subject S902/R2273/JCK [091-060]) |
| 4-9-2003 | IND | Submission: IND Safety Reports: Initial Report (Subject S027/R0952/BLJ [091-050]), Follow Up Report (Subject S010/R0317/FMF [091-050]) |
| 4-15-2003 | IND | Submission: IND Safety Reports: Follow Up Report (Subject S024/R0970/MJW [091-050]). Follow Up Report (Subject S063/R0968/MAO [091-050]) |
| 4-16-2003 | IND | Submission: IND Safety Report: Follow Up Report (Subject S065/R0436/EAM [091-050]), Correction to a Follow Up Report (Serial No. 164) |
| 4-18-2003 | IND | Submission: IND Safety Report: Follow up report (Subject S014/R0923/DCR) study 091-050 |
| 4-22-2003 | IND | Submission: IND Safety Reports: Initial Report (Subject S001/R0474/JDO [091-050]), Initial Report (Subject S502/R2341/REH [091-060]) |
| 4-23-2003 | IND | Submission: IND Safety Report: Follow Up Report (Subject S504/R2281/DHK [091-060]) |
| 4-24-2003 | IND | General Correspondence: Safety Surveillance System |
| 4-25-2003 | IND | Submission: IND Safety Report: Follow Up Report (Subject S029/R5295/TMM) |
| 4-30-2003 | IND | Submission: IND Safety Report: 7-Day Fax Transmission (Subject S017/R5283/ERR [091-051]) |
| 5-1-2003 (A) | IND | Protocol Amendment: New Investigators (091-014, 091-051, 091-060) |
| 5-1-2003 (B) | IND | Submission: IND Safety Report: Follow Up Report (Subject S001/R0474/JDO [091-050]) |
| 5-2-2003 | IND | Submission: IND Safety Report: Follow Up Report (Subject S502/R2341/REH [091-060]) |
| 5-9-2003 | IND | Submission: IND Safety Reports: Initial Report (Subject S015/R0501/EFT [091-050]), Follow Up Report (Subject S027/R0952/BLJ [091-050]) |
| 5-13-2003 (A) | IND | Submission: IND Information Amendment: Pharmacology / Toxicology. 4 nonclinical studies |
| 5-13-2003 (B) | IND | Submission: IND Safety Reports: Follow Up Report (Subject S501/R2028/RDW [091-060]), Follow Up Report (Subject S027/R0952/BLJ [091-050]) |

| Date | Type | Activity |
|---|---|---|
| 5-15-2003 | IND | Communication from Sepracor to FDA providing follow-up IND Safety Report subject (S017/R5283/ERR) study 091-051 |
| 5-16-2003 (A) | IND | Submission: IND Safety Reports: Follow-up Reports<br>7-Day fax transmission – follow-up IND Safety Report subject (S017/R5283/ERR) study 091-051 and Follow-up Report Subject (S015/R0501/EFT) study 091-050 |
| 5-16-2003 (B) | IND | Submission: IND Safety Report: Initial Report (Subject S512/R2145/MDM [091-060]) |
| 5-19-2003 | IND | Submission: IND Safety Report: Follow Up Report (Subject S010/R5151/FAE [091-051]) |
| 5-20-2003 (A) | IND | Communication from Sepracor to FDA providing initial IND Safety Report (7-day Fax Transmission) study 091-051, subject (S023/R5321/EAW) |
| 5-20-2003 (B) | IND | Submission: IND Safety Reports: Initial Report (7-day Fax Transmission) study 091-051, subject (S023/R5321/EAW) and Follow-up report study 091-051, Subject (S029/R5295/TMM) |
| 5-22-2003 | IND | Submission: IND Safety Reports: Follow Up Report (Subject S007/R0950/RAL [091-050]), Follow Up Report (Subject S001/R5299/WCM [091-051]) |
| 5-27-2003 | IND | Submission: IND Safety Report: Initial Report (Subject S901/R2072/H-J [091-060]), Follow Up Report (Subject S001/R0474/JDO [091-050]) |
| 6-4-2003 | IND | Submission: IND Annual Report (April 1, 2002 through March 31, 2003 |
| 6-5-2003 (A) | IND | Protocol Amendment: New Investigators (091-051, 091-060) |
| 6-5-2003 (B) | IND | Telephone discussion between Sepracor and FDA regarding Serial No. 169 which provided information on the approach to the Safety Surveillance utilized in the clinical development process |
| 6-10-2003 | IND | Submission: IND Safety Reports: Initial Report (Subject S537/R2319/JCC) Follow-up Report (Subject S001/R5004/EMW) Follow-up Report (Subject S001/R0474/JDO) studies –050, -051 and -060 |
| 6-11-2003 | IND | Submission: IND Safety Report: Follow-up report (Subject S022/R0349/NSD) study 091-050 |
| 6-13-2003 | IND | Submission: IND Safety Reports: Initial Report (Subject S002/R5868/DLH) Follow-up Report (Subject S012/R5242/PJS) both are from study 091-051 |
| 6-17-2003 | IND | Submission: IND Safety Reports: Initial Report (Subject S019/R5344/MVR [091-051]) |
| 6-18-2003 | IND | Submission: IND Safety Report: Initial Report (Subject S026/R5385/JRW [091-051]) |
| 6-19-2003 | IND | Telephone discussion between Sepracor and FDA regarding FDA's comments on the safety surveillance submitted in Serial No. 169 |
| 6-23-2003 | IND | Submission: IND Safety Reports: Initial Report (Subject S066/R0974/BGT [091-050]), Follow Up Report (Subject S504/R2281/DHK [091-060]) |
| 6-25-2003 | IND | Submission: IND Safety Reports: Initial Reports (S006/R5357/BJC [-051], S502/R2257/RDE [-060], S019/R0523/P-K [-050]) |
| 6-26-2003 (A) | IND | Protocol Amendment: New Investigators: 091-016, 091-051, 091-060 |
| 6-26-2003 (B) | IND | Submission: IND Safety Report: Follow-up Report (Subject S537/R2319/JCC [091-060]) |

| Date | Type | Activity |
|---|---|---|
| 6-26-2003 (C) | IND | Telephone discussion between Sepracor and FDA regarding Safety Surveillance Comments |
| 7-1-2003 | IND | Submission: IND Safety Reports: Follow up Report (Subject S008/R0205/RMS) study –014 and Initial Report (Subject S509/R2186/GSB) study -060 |
| 7-3-2003 | IND | Submission: IND Safety Reports: Follow up Report (Subject S017/R5283/ERR) study 091-051, Initial Report (Subject S501/R2246/JFG) study 091-060 |
| 7-8-2003 | IND | Submission: IND Safety Reports: 1 Initial Report (S014/R0975/CLC) study 091-050 2 Follow up Reports: (S002/R5868/DLH) (S019/R5344/MVR) study 091-051 1 Follow-up Report (S901/R2072/H-J) study 091-060 |
| 7-17-2003 (A) | IND | Communication from Sepracor to FDA providing IND Safety Report: Initial Report: (7-Day Fax Transmission) subject S026/R5229/SEP study 091-051 |
| 7-17-2003 (B) | IND | Submission: IND Safety Reports: 7-Day Fax Transmission: Subject S026/R5229/SEP study 091-051, Follow up Report: Subject S026/R5229/SEP study 091-051, Follow-up Report Subject S014/R095/CLC study 091-050 |
| 7-18-2003 | IND | Submission: IND Safety Report: Follow up Report<br>Subject (S002/R5868/DLH) Study 091-051 |
| 7-23-2003 (A) | IND | Communication from Sepracor to FDA providing IND Safety Report: Initial Report: 7-Day Fax Transmission (Subject S907/R2088/CWH) study 091-060 |
| 7-23-2003 (B) | IND | Submission: IND Safety Report: Initial Report: (Subject S905/R2348/BMJ), Initial Report: (7-Day Fax: Subject S907/R2088/CWH) study 091-060 |
| 7-28-2003 (A) | IND | Telephone discussion between Sepracor and FDA regarding the status of the letter from FDA concerning comments on Safety Surveillance |
| 7-28-2003 (B) | IND | Information Amendment: Chemistry, Manufacturing, and Controls |
| 7-29-2003 | IND | Submission: IND Safety Report: Initial Report (Subject S931/R2585/JRL) Follow Up Report (Subject S502/R2257/RDE), Follow Up Report (Subject S501/R2246/JFG) study 091-060 |
| 7-30-2003 (A) | IND | Submission: IND Safety Report: Initial Report (Subject S007/R5418/RAH [091-051]), Initial Report (Subject S501/R2520/L-B [091-060]) |
| 7-30-2003 (B) | IND | General Correspondence: USAN Name (Change from (R,R)-Formoterol L-tartrate to Arformoterol tartrate) |
| 7-31-2003 (A) | IND | Communication from Sepracor to FDA providing IND Safety Report: Follow Up: 7-Day Fax Transmission (Subject S007/R5418/RAH) study 091-051 |
| 7-31-2003 (B) | IND | Submission: IND Safety Report: Follow Up Report: (7-Day Fax: Subject S007/R5418/RAH), Follow Up Report: (Subject S004/R5125/DLB), study 091-051 |
| 8-1-2003 | IND | Submission: IND Safety Reports: Follow-up Report (Subject S066/R0974/BGT) study 091-050 Follow-up Report (Subject S002/R5868/DLH) Study 091-051 |
| 8-5-2003 | IND | Protocol Amendment: New Investigators (091-051 and 091-060) |
| 8-6-2003 | IND | Submission: IND Safety Report: Follow Up Report (Subject S905/R2348/BJM [091-060]) |
| 8-7-2003 | IND | Submission: IND Safety Report: Initial Report (Subject S001/R5334/PSJ [091-051]) |

| Date | Type | Activity |
|---|---|---|
| 8-11-2003 | IND | Submission: IND Safety Reports: Initial Report (Subject S522/R2065/A-S [-060]), Follow Up Reports: (Subject S931/R2585/JRL [-060]), (Subject S907/R2088/CWH [-060]), (Subject S049/R0428/L-F [091-050]) |
| 8-18-2003 | IND | General Correspondence: Open Label Comparator Adverse Event (Subject S507/R2368/WMF) 091-060 |
| 8-19-2003 (A) | IND | Submission: IND Safety Reports: Follow Up Reports (Subject S905/R2348/BMJ [-060]), Subject (S509/R2186/GSB [-060]) |
| 8-19-2003 (B) | IND | FDA response to Submission of 4/24/03, Serial No. 169, General Correspondence: Safety Surveillance System |
| 8-19-2003 (C) | IND | Fax from FDA of the Response to Submission of 4/24/03, Serial No. 169, General Correspondence: Safety Surveillance System |
| 8-21-2003 | IND | Protocol Amendment: Revised 1572's (Protocols 091-013, 091-014, 091-015, 091-016, 091-051, 091-060) |
| 8-25-2003 | IND | Submission: IND Safety Report: Follow Up Report (Subject S001/R5334/PSJ [091-051]) |
| 8-28-2003 (A) | IND | Submission: IND Safety Report: Initial Report (Subject S909/R2214/CWM) study 091-060 |
| 8-28-2003 (B) | IND | Information Amendment: Revised Investigator's Brochure |
| 9-2-2003 | IND | Submission: IND Safety Report: Follow Up Report (Subject S007/R5418/RAH [091-051]) |
| 9-4-2003 (A) | IND | Communication from Sepracor to FDA providing IND Safety Report: Initial Report: 7-Day Fax Transmission (Subject S037/R5466/R-L [091-051]) |
| 9-4-2003 (B) | IND | Submission: IND Safety Report: Initial Report (7-Day Fax: Subject S037/R5466/R-L [091-051]) |
| 9-8-2003 | IND | IND Safety Report: Initial Report (Subject S502/R2341/REH [091-060]) |
| 9-9-2003 (A) | IND | Protocol Amendment: Revised Protocol (091-015) |
| 9-9-2003 (B) | IND | Submission: IND Safety Reports: Follow Up Report (Subject S931/R2585/JRL [-060]), Follow Up Report (Subject S019/R0523/P-K [-050]) |
| 9-10-2003 | IND | Submission: IND Safety Report: Initial Report (Subject S507/R2525/M-B [091-060]) |
| 9-11-2003 | IND | Submission: IND Safety Report: Initial Report (Subject S906/R2513/OBG [091-060]) |
| 9-12-2003 | IND | Submission: IND Safety Reports: Initial Report (Subject S501/R2282/PAD [091-060]), Initial Report (Subject S904/R2251/CJT [091-060]) |
| 9-17-2003 (A) | IND | Submission: IND Safety Reports: Follow Up Report (Subject S909/R2214/CWM [091-060]) |
| 9-17-2003 (B) | IND | Protocol Amendment: New Protocol (091-026), New Investigators. (-026, -051) Revised Protocols. (-060) |
| 9-18-2003 | IND | Submission: IND Safety Reports: Initial Report (MFR 2003SP000002 [-060]), Initial Report (MFR 2003SP000001 [-051]) |
| 9-19-2003 | IND | Submission: IND Safety Reports: Initial Report (MFR 2003SP000003 [-051]), Initial Report (MFR 2003SP000004 [-060]) |

| Date | Type | Activity |
|---|---|---|
| 9-23-2003 (A) | IND | Submission: IND Safety Reports: Initial Report (MFR 2003SP000005 [-060]) |
| 9-23-2003 (B) | IND | Information Amendment: Pharmacology/Toxicology |
| 9-25-2003 | IND | Submission: IND Safety Reports: Follow Up Report (Subject S502/R2341/REH [-060]) |
| 9-30-2003 | IND | Submission: IND Safety Reports: Follow-up Reports: (MFR 2003SP000002) and (MFR 2003SP000001) studies 091-051 and 091-060 |
| 10-1-2003 (A) | IND | Communication from Sepracor to FDA providing IND Safety Report: 7-Day Fax Transmission (MFR 2003SP000004) study 091-060 |
| 10-1-2003 (B) | IND | Submission: IND Safety Report: Follow-up Report s (7-Day Fax Transmission) (MFR 2003SP000004) study 091-060 and (MFR 2003SP000003) study 091-051 |
| 10-2-2003 | IND | Submission: IND Safety Reports: Follow Up Reports: (Subject S501/R2282/PAD [-060]), (Subject S065/R0436/EAM, Subject S007/R0950/RAL, Subject S018/R0122/HTH [-050]) |
| 10-3-2003 | IND | Submission: IND Safety Reports: Initial Report (MFR 2003SP000008 [-060]), Follow Up Report (MFR 2003SP000005 [-060]) |
| 10-6-2003 (A) | IND | Information Amendment: CMC |
| 10-6-2003 (B) | IND | Protocol Amendment: Revised Protocol Version 2.0 091-051 |
| 10-7-2003 | IND | Submission: IND Safety Report: Initial Report (MFR 2003SP000010 [-060]) |
| 10-9-2003 | IND | Submission: IND Safety Report: Follow Up Report (Subject S037/R5466/R-L [091-051]) |
| 10-10-2003 (A) | IND | Submission: ND Safety Report: Follow Up Report (MFR 2003SP000003-fu2 [091-051]) |
| 10-10-2003 (B) | IND | General Correspondence: Safety Surveillance System |
| 10-14-2003 | IND | Submission: IND Safety Report: Follow Up Report (MFR 2003SP000004-fu2 [091-060]) |
| 10-16-2003 (A) | IND | Submission: IND Safety Report: Follow Up Report (Subject S907/R2088/CWH [091-060]) |
| 10-16-2003 (B) | IND | Protocol Amendment: New Investigators (091-026) |
| 10-23-2003 | IND | Submission: IND Safety Reports: Initial Report (MFR 2003SP000013 [091-051]), Initial Report (MFR 2003SP000014 [091-060]) |
| 10-24-2003 | IND | Submission: IND Safety Report: Follow Up Report (Subject S906/R2513/OBG [091-060]) |
| 10-27-2003 | IND | Submission: IND Safety Report: Initial Report: MFR. No. 2003SP000016 study 091-060 |
| 10-31-2003 | IND | Submission: IND Safety Reports: Initial Report (MFR 2003SP000022 [091-060]), Initial Report (MFR 2003SP000024 [091-051]) |
| 11-3-2003 | IND | Submission: IND Safety Report: Follow Up Report (MFR 2003SP000008 [091-060]) |
| 11-7-2003 | IND | Submission: IND Safety Reports: Follow Up Reports to Unblinding (091-050) |
| 11-12-2003 (A) | IND | Protocol Amendment: New Investigators (091-026) |

| Date | Type | Activity |
|---|---|---|
| 11-12-2003 (B) | IND | Submission: IND Safety Reports: Follow Up Reports (MFR 2003SP000010-FU1, 2003SP000022-FU1 [091-060]), Follow Up Report (MFR 2003SP000024-FU1 [091-051]) |
| 11-17-2003 | IND | Submission: IND Safety Reports: Initial Reports (MFR 2003SP000032, 2003SP000037 [091-060]) |
| 11-18-2003 | IND | General Correspondence: Request for Type C Meeting |
| 11-19-2003 | IND | Submission: IND Safety Reports: Initial Reports (MFR 2003SP000031, 2003SP000034 [091-060]) |
| 11-21-2003 | IND | Submission: IND Safety Reports: Initial Reports (MFR 2003SP000035 [091-060]) |
| 11-25-2003 | IND | Submission: IND Safety Reports: Initial Reports (MFR 2003SP000036 [-051], MFR 2003SP000040 [-051], MFR 2003SP000041 [-060], MFR 2003SP000045 [-060]), Follow Up Report (MFR 2003SP000031 [-060]) |
| 12-2-2003 | IND | Request by Sepracor for Type C Meeting –Follow-up |
| 12-3-2003 (A) | IND | Submission: IND Safety Report: Initial Report (MFR 2003SP000046 [-051]) |
| 12-3-2003 (B) | IND | Communication from FDA to Sepracor regarding the scheduling of the Type C Meeting |
| 12-5-2003 | IND | Submission: IND Safety Reports: Initial Reports (MFR 2003SP000051, 2003SP000052 [091-060]) |
| 12-9-2003 | IND | Submission: IND Safety Report: Initial Report (MFR 2003SP000053 [091-051]) |
| 12-10-2003 (A) | IND | Communication from Sepracor to FDA providing Type C Meeting- Draft Questions |
| 12-10-2003 (B) | IND | General Correspondence: Draft Questions for the Type C Meeting |
| 12-12-2003 | IND | Protocol Amendment: New Investigators 091-026 |
| 12-15-2003 | IND | Submission: IND Safety Reports: Follow Up Report (Subject S904/R2251/CJT [091-060]) |
| 12-16-2003 | IND | Submission: IND Safety Report: Follow Up Report (MFR 2003SP00002 [091-060]) |
| 12-17-2003 | IND | Submission: IND Safety Report: Initial Report (MFR 2003SP000055 [091-060]), Follow Up Report (MFR 2003SP000052-FU1 [091-060], MFR 2003SP000040-FU1 [091-051]) |
| 12-19-2003 | IND | Submission: IND Safety Reports: Initial Report (MFR 2003SP000057[091-051]), Initial Report (MFR 2003SP000059[091-051]), Follow Up Report (MFR 2003SP000053 [091-051]), Follow Up Report (MFR 2003SP000045 [091-060]), Follow Up Report (MFR 2003SP000041 [091-060]) |
| 12-22-2003 | IND | Submission: IND Safety Reports: Follow Up Report (S037/R5466/R-L [091-051]) |
| 12-23-2003 (A) | IND | Submission: Response to FDA Request for Information: Safety Surveillance System |
| 12-23-2003 (B) | IND | Submission: IND Safety Reports: Initial Report (MFR 2003SP000062 [091-026], Follow Up Report (Subject S906/R2513/OBG [091-060]) |
| 1-6-2004 | IND | Communication between Sepracor and FDA regarding Type C Meeting Package, the location of the Meeting, and the submission of Reponses to FDA Request for Information |
| 1-9-2004 | IND | Communication from Sepracor to FDA regarding Type C Meeting Package |

| Date | Type | Activity |
|---|---|---|
| 1-12-2004 (A) | IND | Submission: IND Safety Report: Initial Report (MFR 2003SP000065 [091-060]) |
| 1-12-2004 (B) | IND | Follow-up communication regarding Type C meeting package |
| 1-14-2004 (A) | IND | Communication from Sepracor to FDA providing IND Safety Report: Initial Report - 7-Day Fax Transmittal (MFR. 2004SP000006) |
| 1-14-2004 (B) | IND | Submission: IND Safety Report: 7-Day (MFR. 2004SP000006) |
| 1-14-2004 (C) | IND | General Correspondence: Type C Meeting Information Package |
| 1-19-2004 (A) | IND | Submission: IND Safety Reports: Initial Reports (MFR 2004SP000001, 2004SP000004 [091-060]), Initial Report (MFR 2004SP000006 [091-051]) |
| 1-19-2004 (B) | IND | Submission: IND Safety Reports: Initial Reports (MFR 2004SP000002, 2004SP000005), Follow-Up Report (MFR 2003SP000062 [091-026]) |
| 1-20-2004 | IND | Protocol Amendment: Amendment 2, Revised Protocol, New Investigators, Revised 1572's for protocol 091-026 |
| 1-22-2004 | IND | Submission: IND Safety Reports: Initial Reports (MFR 2004SP000009, 2004SP000011 [091-060]) |
| 1-23-2004 | IND | Communication from FDA to Sepracor providing list of attendees for the February 9, 2004 meeting between Sepracor and FDA |
| 1-26-2004 | IND | Information Amendment: Pharmacology/Toxicology (090-836) |
| 1-27-2004 | IND | Submission: IND Safety Reports: Initial Report (MFR 2004SP000013 [091-060]), Initial Report (MFR 2004SP000015 [091-051]) |
| 1-29-2004 | IND | Follow-up communication regarding the list of attendees from FDA for the Type C Guidance Meeting on February 9, 2004 |
| 1-30-2004 | IND | Submission: IND Safety Reports: Initial Report (MFR 2004SP000016 [091-060]), Initial Report (MFR 2004SP000017 [091-026]), Follow-Up Report (MFR 2004SP000005-FU1[091-026]) |
| 2-3-2004 (A) | IND | FDA Pharm/Tox Reviewer Request for Information regarding the amount of desformoterol that will typically be in the drug substance and drug product referred to in study 090-836 (Serial No. 277) |
| 2-3-2004 (B) | IND | Response to FDA Pharm/Tox Reviewer's Earlier Request for Information |
| 2-5-2004 | IND | Submission: IND Safety Reports: Initial Report (MFR 2004SP000020 [091-060]), Follow-Up Report (MFR 2003SP000036-FU1 [091-051]) |
| 2-6-2004 (A) | IND | Type C Meeting Follow-up |
| 2-6-2004 (B) | IND | Communication from Sepracor to FDA providing the list of Sepracor attendees for the Type C Meeting on February 9, 2004 |
| 2-10-2004 | IND | Submission: IND Safety Reports: Follow-Up Report (MFR 2003SP000057-FU1[091-051]), Follow-Up Report (MFR 2004SP000013-FU1[091-060]) |

| Date | Type | Activity |
|---|---|---|
| 2-13-2004 | IND | Submission: IND Safety Reports: Follow-Up Report (S012/R5093/CJW [091-051]), |
| 2-19-2004 | IND | Submission: IND Safety Reports: Initial Report (2004SP000025 [091-060]), Follow-Up Report (2004SP000011-FU1 [091-060]) |
| 2-20-2004 | IND | Submission: IND Safety Reports: Follow-Up Report (2004SP000002-FU1 [091-026]) |
| 2-24-2004 | IND | Protocol Amendment: Protocol 091-026, New Investigators (4) |
| 2-25-2004 | IND | Submission: IND Safety Reports: Initial Report (2004SP000027 [091-026]), Initial Report (2004SP000028 [091-060]), Follow-Up Report (2004SP000009-FU1 [091-060]) |
| 2-27-2004 | IND | Official FDA Meeting Minutes from the Type C Meeting Between Sepracor and FDA on February 9, 2004 |
| 3-2-2004 | IND | Submission: IND Safety Reports: Initial Report (2004SP000035 [091-060]) |
| 3-5-2004 | IND | Submission: IND Safety Reports: Follow-Up Report (S026/R5385/JRW [091-051]), |
| 3-11-2004 | IND | Submission: IND Safety Reports: Initial Report (2004SP000038 [091-026]) |
| 3-17-2004 | IND | Submission: IND Safety Reports: Initial Report (2004SP000041 [091-060]) |
| 3-18-2004 | IND | Submission: IND Safety Reports: 1-Initial Report (2004SP000045) 2- Follow-up (2004SP000028) |
| 3-24-2004 | IND | Information Amendment: Pharmacology/ Toxicology |
| 3-26-2004 | IND | Submission: IND Safety Reports: Initial Report (2003SP000016-FU1 [091-060]) |
| 3-30-2004 (A) | IND | Communication from Sepracor to FDA providing a fax copy of IND Safety Reports: 7-Day Faxes: Initial Report (2004SP000054 [091-060]), Follow-Up Report (2004SP000011-FU2 [091-060]) |
| 3-30-2004 (B) | IND | Submission: IND Safety Reports: 7-Day Faxes: Initial Report (2004SP000054 [091-060]), Follow-Up Report (2004SP000011-FU2 [091-060]) |
| 3-31-2004 | IND | Submission: IND Safety Reports: Initial Report (2004SP000050 [091-026]), Initial Report (2004SP000052 [091-051]), Follow-Up Report (2004SP000039-FU1 [091-026]) |
| 4-6-2004 (A) | IND | Protocol Amendment: Change in Protocol (Amendment No. 3, Protocol 4.0 [091-026]) |
| 4-6-2004 (B) | IND | Submission: IND Safety Reports: Initial Report (2004SP000056 [091-026]) |
| 4-8-2004 | IND | Submission: IND Safety Reports: Initial Report (2004SP000057 [091-026]) |
| 4-13-2004 | IND | Submission: IND Safety Reports: Initial Report (2004SP000061 [091-026]) |
| 4-16-2004 | IND | Submission: IND Safety Reports: Initial Report (2004SP000069 [091-026]) |
| 4-20-2004 | IND | Submission: IND Safety Reports: Follow-Up Report (2003SP000065-FU1 [091-060]) |
| 4-22-2004 | IND | Submission: IND Safety Reports: Initial Report (2004SP000071 [091-060]) |
| 4-26-2004 | IND | Submission: IND Safety Reports: Follow-Up (2004SP000050-FU1 [091-026]) |
| 5-3-2004 | IND | Submission: IND Safety Reports: Follow-Up Report (2003SP000046-FU1 [091-051]), Follow-Up Report (2004SP000041-FU1 [091-060]) |
| 5-11-2004 | IND | Submission: IND Safety Reports: Follow-Up (2004SP000017-FU1 [091-026]) |
| 5-13-2004 | IND | Submission: IND Safety Reports: Follow-Up (2004SP000052-FU1 [091-051]) |

| Date | Type | Activity |
|---|---|---|
| 5-18-2004 | IND | Submission: Resubmission of IND Safety Report (2004SP000052-FU1) to replace report submitted in Serial No. 306 |
| 5-20-2004 (A) | IND | Submission: IND Safety Report: Follow-Up Report (MFR 2004SP000069-FU1 [091-026]) |
| 5-20-2004 (B) | IND | General Correspondence: Type C Meeting Follow-Up |
| 5-20-2004 (C) | IND | Communication from Sepracor to FDA providing a fax copy of Serial No. 309, General Correspondence: Type C Meeting Follow-Up |
| 5-20-2004 (D) | IND | Communication from FDA to Sepracor providing reviewer comments on submission (General Correspondence: Type C Meeting Follow-Up) serial no. 309 dated 5/20/2004 |
| 5-25-2004 | IND | Submission: IND Safety Report: Initial Report (MFR 2004SP000109 [091-051]) |
| 5-28-2004 | IND | Communication from FDA to Sepracor granting request for Type C Meeting on JUNE 15, 2004 |
| 6-1-2004 | IND | Submission: IND Safety Reports: Follow Up Reports (MFR 2004SP000051-FU1 [-060], 2004SP000011-FU3 [-060], 091051_030528_1 [-051]) |
| 6-3-2004 (A) | IND | Submission: IND Safety Reports: Initial Report (MFR 2004SP000116 [-060]) |
| 6-3-2004 (B) | IND | Several communications between 5/20/2004 and 6/3/2004:<br>to notify FDA that a desk copy of the submission had been faxed to FDA<br>to confirm FDA received the fax and to try to determine a teleconference time and date<br>to schedule a teleconference time and date<br>to try and finalize teleconference time and date<br>to inform FDA of call number for teleconference and Sepracor list of attendees |
| 6-7-2004 | IND | Protocol Amendment: New Protocol, New Investigators (091-007), Protocol Synopsis (091-018) |
| 6-10-2004 | IND | Submission: IND Safety Report: Initial Report (MFR 2004SP000122 [091-060]) |
| 6-15-2004 (A) | IND | Communication from FDA to Sepracor regarding cancellation of June 15, 2004 teleconference |
| 6-15-2004 (B) | IND | Submission: IND Safety Reports: Follow-Up Report (S091060_030330_1-FU2 [-060]), Follow-Up Report (SU091051_021125_1-FU5 [-051]) |
| 6-16-2004 | IND | Submission: IND Safety Report: Follow-up Report (MFR. No. 2003SP000059-FU1) study 091-051 |
| 6-21-2004 | IND | Submission: IND Safety Reports: Follow-Up Report (MFR 2004SP000061-FU1 [091-026]), Follow-Up Report (SU091051_030424_1-FU3 [091-051]) |
| 6-22-2004 (A) | IND | Submission: IND Safety Report: Follow-Up Report (MFR 2004SP000057-FU1 [091-026]) |
| 6-22-2004 (B) | IND | General Correspondence: Clarification of Information |
| 6-25-2004 | IND | Request by FDA for Feedback on Protocol 091-007 (submitted in Serial #313 on 07 June 04) |
| 6-29-2004 (A) | IND | Information Amendment: CMC |

| Date | Type | Activity |
|---|---|---|
| 6-29-2004 (B) | IND | Protocol Amendment: New Investigator (090-007) |
| 7-6-2004 (A) | IND | Submission: IND Safety Report: Follow-up report (091-026) MFR. 2004SP000056-FU1 |
| 7-6-2004 (B) | IND | Submission: IND Safety Report: Follow-up report (091-060) MFR. 2004SP000045-FU1 |
| 7-12-2004 (A) | IND | Submission: IND Safety Report: Initial report (091-060) MFR. 2004SP000146 |
| 7-12-2004 (B) | IND | Submission: IND Safety Report: Follow-Up report (091-060) MFR. 2003SP000034-FU1 |
| 7-13-2004 | IND | Submission: IND Safety Report: Follow-Up reports (091-060) MFR. 2003SP000014-FU1, 2004SP000013-FU2, 2004SP000016-FU1 |
| 7-14-2004 | IND | Request by Sepracor for feedback on Protocol 091-007 (submitted in Serial #313 on 07 June 04) |
| 7-15-2004 | IND | Submission: IND Safety Reports: Follow-Up Reports (Unblinding of Study 091-051) |
| 7-16-2004 (A) | IND | Submission: IND Safety Report: Follow-Up Reports (MFR SU091060_030619_1-FU2) |
| 7-16-2004 (B) | IND | Submission: IND Annual Report (April 1, 2003 through March 31, 2004) |
| 7-20-2004 | IND | Communication from FDA to Sepracor providing Clinical Pharmacology and Biopharmaceutics comments regarding Protocol 091-007. |
| 7-21-2004 | IND | Submission: IND Safety Reports: Initial Report (MFR 2004SP000154 [-060]), Follow-Up Report (MFR 2004SP000146-FU1 [-060]), Follow-Up Report (MFR 2004SP000056-FU2) |
| 7-23-2004 | IND | General Correspondence: Authorization to Cross Reference IND 55,302 |
| 7-26-2004 | IND | Protocol Amendment: New Protocol, New Investigators (2) 091-018 |
| 7-28-2004 | IND | Submission: IND Safety Report: Follow-Up report (091-060) MFR. 2003SP000055-FU1 |
| 7-29-2004 | IND | Submission: IND Safety Report: Follow-Up report (091-051) MFR. 2004SP000015-FU2 |
| 8-3-2004 | IND | Submission: IND Safety Report: Initial Report (091-060) MFR. 2004SP0000167 |
| 8-6-2004 | IND | Protocol Amendment: Change in Protocol (091-007) |
| 8-12-2004 | IND | Submission: IND Safety Report: Follow-Up report (091-060) MFR. 2004SP000154-FU1 |
| 8-16-2004 | IND | Submission: Information Amendment: Pharmacology/Toxicology (4 Volumes) |
| 8-24-2004 | IND | Submission: IND Safety Report: Follow-Up report (091-060) MFR. 2004SP000009-FU2 |
| 9-2-2004 | IND | Submission: IND Safety Report: Follow-Up report (091-060) MFR. 2004SP000025-FU1 |
| 9-14-2004 | IND | Submission: IND Safety Reports: 11 Follow-up reports 091-026 unblinding |
| 9-15-2004 | IND | Submission: IND Safety Reports: Follow-up reports: 091-060 (MFR 2004SP000004 and 2004SP000167) |
| 9-28-2004 (A) | IND | Submission: IND Safety Report: Follow-up report: 091-021 (MFR 2004SP000017FU3) |

| Date | Type | Activity |
|---|---|---|
| 9-28-2004 (B) | IND | Communication from Sepracor to FDA regarding the change in the contact person for the CMC |
| 10-4-2004 | IND | IND Safety Report: Follow-up Report (MFR 2003SP000051) Study 091-060 |
| 10-14-2004 | IND | Protocol Amendment: Revised forms FDA 1572 (2) for protocol 091-018 |
| 10-20-2004 | IND | Submission: IND Safety Report: Initial Report (MFR 2004SP000219) |
| 10-21-2004 | IND | Information Amendment: Pharmacology/Toxicology (17 volumes) |
| 10-28-2004 | IND | Submission: IND Safety Report: Initial Report (MFR 2004SP000242) |
| 11-2-2004 | IND | Communication between Sepracor and FDA regarding submission of electronic SAS Datatsets |
| 11-3-2004 | IND | Information Amendment: Pharmacology/Toxicology (20 volumes) |
| 11-4-2004 | IND | Submission: IND Safety Report: Follow-Up Report (MFR 2004SP0000045-FU2) |
| 11-8-2004 | IND | Submission: IND Safety Report: Follow-Up Report (MFR 2003SP0000008-FU2) |
| 11-10-2004 | IND | Submission: IND Safety Report: Follow-Up Report (MFR 2004SP0000242-FU1) |
| 11-17-2004 (A) | IND | Submission: IND Safety Report: Follow-Up Report -060 (2004SP000035-FU1) |
| 11-17-2004 (B) | IND | Information Amendment: Clinical<br>(study 091-007) |
| 11-17-2004 (C) | IND | Communication from Sepracor to FDA regarding the status of carcinogenicity report review and enrollment of 091-007 |
| 11-17-2004 (D) | IND | Communication from Sepracor to FDA providing a fax copy of submission Serial No. 354, Information Amendment: Clinical sent to FDA on this date |
| 11-19-2004 | IND | Protocol Amendment: Revised forms FDA 1572 for protocols 091-007, 091-060 |
| 12-02-2004 | IND | Information Amendment: Pharmacology/Toxicology (3 volumes) |
| 12-03 and 12-06-2004 | IND | Communication from FDA to Sepracor regarding enrollment status of 091-007 and request by FDA for electronic carcinogenicity datasets |
| 12-09-2004 | NDA | General Correspondence: Type B Mtg - Pre-NDA Meeting Request by Sepracor to Review Arformoterol Clinical and Nonclinical Development Program |
| 12-13-2004 (A) | NDA | Communication between Sepracor and FDA regarding the request for pre-NDA meeting |
| 12-13-2004 (B) | NDA | Communication from Sepracor to FDA providing a copy of request for pre-NDA meeting |
| 12-14-2004 | IND | Information Amendment: Pharmacology/Toxicology |
| 12-20-04 (A) | IND | IND Safety Report: Initial Report -060 (2004SP000313) |
| 12-20-2004 (B) | NDA | Communication from FDA to Sepracor granting the meeting |
| 12-21-2004 | NDA | Communication between Sepracor and FDA regarding scheduling of the meeting |
| 01-03-2005 | NDA | General Correspondence: Request for CMC Pre-NDA Meeting (Type B) |

| Date | Type | Activity |
|---|---|---|
| 1-4-2005 (A) | NDA | Communication between Sepracor and FDA regarding the pre-NDA meeting request (Serial No. 360) |
| 1-4-2005 (B) | NDA | Communication from Sepracor to FDA providing request for CMC pre-NDA Meeting |
| 1-11-2005 | NDA | Communication from FDA to Sepracor regarding grant of the CMC pre-NDA meeting |
| 1-12-2005 | IND | Protocol Amendment: Revised forms FDA 1572 for protocol 091-007 |
| 1-12-2005 (A) | NDA | Communication from FDA to Sepracor providing a list of FDA attendees |
| 1-12-2005 (B) | NDA | Communication from FDA to Sepracor regarding grant of the meeting, with a list of FDA attendees |
| 1-20-2005 | IND | Protocol Amendment: New Investigator (091-007) Amendment 1 and Revised Protocol Version 2.0 (091-018) |
| 1-28-2005 | NDA | General Correspondence: Type B Meeting Information Package |
| 1-31-2005 | NDA | General Correspondence: Type B (CMC) Meeting Information Package |
| 2-1-2005 | IND | Protocol Amendment: New Investigators (091-060) |
| 2-11-2005 | NDA | Communication from FDA to Sepracor regarding the CMC preNDA and the clinical/nonclinical preNDA meetings |
| 2-28-2005 (A) | NDA | General Correspondence: Corrections to Type B Meeting Information Package |
| 2-28-2005 (B) | NDA | Communication from Sepracor to FDA providing a fax copy of corrections to Type B Meeting Information Package |
| 3-1-2005 | IND | Communication from Sepracor to FDA regarding the change in the contact person for IND 55,302 |
| 3-4-2005 (A) | NDA | FDA requested Fax number for Ms. Elkins to send FDA responses to CMC PreNDA meeting questions |
| 3-4-2005 (B) | NDA | FDA response to PreNDA meeting package questions (Clinical/Nonclinical) |
| 3-4-2005 (C) | NDA | FDA response to PreNDA CMC meeting package questions |
| 3-4-2005 (D) | NDA | FDA response to the PreNDA Clinical/Nonclinical meeting package |
| 3-4-2005 (E) | NDA | Communication between Sepracor and FDA regarding clarification of question 1 and cancellation of the meeting |
| 3-7-2005 | NDA | Request by Sepracor for clarification on the response to Sepracor's Question 1 as presented in the CMC preNDA Meeting Package dated 1/31/2005 |
| 3-8-2005 | NDA | FDA's response to Sepracor's request for clarification on Question 1 as presented in the CMC preNDA Meeting Package dated 1/31/2005 |
| 3-14-2005 (A) | IND | FDA request for information: Serial No. 349, dated 11-3-2004 – missing pages 3284-3482 be sent |

| Date | Type | Activity |
|---|---|---|
| 3-14-2005 (B) | IND | Information Amendment Pharmacology/Toxicology Pages 3284-3423 of Serial #349 |
| 3-18-2005 (A) | IND | Information Amendment: Pharmacology/Toxicology |
| 3-18-2005 (B) | NDA | General Correspondence: Sepracor Meeting Minutes (Clinical/Nonclincal PreNDA Meeting) |
| 3-21-2005 | NDA | Communication between Sepracor and FDA regarding the NDA number for Arformoterol Tartrate Inhalation Solution – the NDA number assigned is 21-912 |
| 3-28-2005 | NDA | Official FDA Meeting Minutes from the March 7, 2005 Formoterol Pre-NDA (Clinical/Nonclinical) Meeting |
| 3-29-2005 | NDA | Communication between Sepracor and FDA regarding the requirements for paper desk copies of Volume 1 of the NDA for Arformoterol. |
| 4-4-2005 | IND | Protocol Amendment: New Protocol, New Investigator (091-019) |
| 4-6-2005 (A) | NDA | Communication from Sepracor to FDA providing Sepracor's Proposals for Integrated Datasets for upcoming NDA for Arformoterol |
| 4-6-2005 (B) | NDA | General Correspondence: Proposals for Integrated Datasets for upcoming NDA for Arformoterol |
| 4-19-2005 | NDA | Request by Sepracor for clarification of the post meeting note race and ethnicity discussion |
| 4-22-2005 | NDA | Communication between Sepracor and FDA regarding the date of ECAC meeting that had been discussed during the pre-NDA meeting |
| 4-29-2005 | IND | Information Amendment: Pharmacology/Toxicology |
| 5-9-2005 | IND | Protocol Amendment: New Investigators (091-019) |
| 5-12-2005 | IND | Final CAC Report for IND 55,302 (Response to carcinogenicity study review) |
| 5-17-2005 | IND | Follow-up Notice of Noncompliance – Site Management Organization Clinical Study 091-050 |
| 5-18-2005 | NDA | General Correspondence: Proposal for inclusion of ECG waveform files from study 091-026 in the NDA |
| 5-24-2005 | IND | Email exchanges between Sepracor and the FDA regarding the submission timing of nonclinical reports to the IND |
| 5-24-2005 | NDA | General Correspondence Request for Clarification of E-CAC Minutes (FDA comments dated 5/12/2005 – concerning studies 090-833 and 090-828) |
| 6-2-2005 | IND | Protocol Amendment: New Investigators (091-019) |
| 6-3-2005 | NDA | Discussion between Sepracor and FDA regarding the status of the Data variability proposal for CRT datasets (submitted 4/6/2005), Desformoterol tox study (submitted 4/29/2005), ECG waveform dataset proposal (submitted 5/18/2005), and ECAC minutes clarification (submitted 5/24/2005) |
| 6-10-2005 (A) | IND | Submission: IND Annual Report (April 1, 2004 through March 31, 2005) |
| 6-10-2005 (B) | NDA | General Correspondence: Request for clarification of Clinical/Nonclinical Pre-NDA Meeting Minutes (information package on ethnicity) |

| Date | Type | Activity |
|---|---|---|
| 6-17-2005 (A) | IND | FDA response to submission of 4/6/2005, serial number 371 General Correspondence: Proposals for Integrated Datasets for upcoming NDA for Arformoterol |
| 6-17-2005 (B) | NDA | Follow-up communication regarding the status of the Ethnicity Submission sent to FDA on 6/10/2005 in response to the Pre-NDA meeting minutes |
| 6-21-2005 | NDA | FDA response to submission of 5/24/2005, serial number 375;<br>General Correspondence Request for Clarification of E-CAC Minutes (FDA comments dated 5/12/2005 – concerning studies 090-833 and 090-828) |
| 6-30-2005 | NDA | General Correspondence: Request for Type A Meeting: Clarification of Pre-NDA Meeting Minutes |
| 7-5-2005 | NDA | Response to May 18, 2005, Serial Number 374 - General Correspondence: Proposal for Inclusion of ECG Waveform Files from Study 091-026 in the NDA Proposal for Inclusion of ECG Waveform Files from Study 091-026 in the NDA |
| 7-7-2005 (A) | NDA | Protocol Amendment: Change in Protocol, New Investigators (091-019) |
| 7-7-2005 (B) | NDA | Information Amendment: Pharmacology/Toxicology: Planned Procedures for Amendment to 2-Year Rat Carcinogenicity Study |
| 7-7-2005 (C) | NDA | Teleconference between FDA and Sepracor regarding the grant of Type A Meeting (Teleconference) and meeting packages |
| 7-11-2005 | NDA | Letter from FDA granting the Type A Meeting (Teleconference) |
| 7-18-2005 | NDA | General Correspondence: Proposal for Content of Labeling in PDF Format |
| 7-19-2005 | NDA | FDA comments concerning Serial No. 381: Information Amendment: Pharmacology/Toxicology: Planned Procedures for Amendment to 2-Year Rat Carcinogenicity Study |
| 7-22-2005 | NDA | Request by Sepracor for a teleconference with the Pharm/Tox Reviewers at FDA to discuss the 2-year rat carcinogenicity study submitted on 7/7/2005 in serial no. 381 |
| 7-26-2005 (A) | NDA | General Correspondence: Type A Meeting Information Package |
| 7-26-2005 (B) | NDA | Communication from Sepracor to FDA fowarding information for use during the teleconference with nonclinical FDA reviewers |
| 7-27-2005 | NDA | FDA response to Sepracor's fax of 7/25/05 concerning the upcoming teleconference to discuss the 2-year rat carcinogenicity study submitted on 7/7/2005 in serial no. 381 |
| 7-29-2005 | NDA | Cancellation of the teleconference requst made by Sepracor on 7/22/2005 |
| 8-10-2005 (A) | NDA | Communication between Sepracor and FDA regarding the teleconference to be held on Aug. 17, 2005. Follow-up on Serial No. 382 (request concurrence on submitting the label in PDF format not SPL format) |
| 8-10-2005 (B) | NDA | Communication by FDA regarding rescheduling of teleconference |
| 8-15-2005 | NDA | Sepracor version of the minutes from the 8/15/2005 teleconference with FDA to discuss ethnicity issues |
| 8-19-2005 (A) | NDA | FDA official meeting minutes from the August 15, 2005 teleconference to discuss ethnicity (reference back to 6/10/2005 submission and 3/7/2005 pre-NDA meeting submission) |

| Date | Type | Activity |
|---|---|---|
| 8-19-2005 (B) | NDA | FDA response to submission of 7/18/2005 concerning SPL |
| 9-8-2005 | IND | Protocol Amendment: New Protocol (091-061), and IB.<br>Information Amendment: CMC—Placebo for active comparator Foradil Aerolizer® |
| 9-30-2005 (A) | NDA | General Correspondence: Proposed Proprietary Trade Name Expede™ |
| 9-30-2005 (B) | IND | Submission: 15-Day IND Safety Report: Initial Report (2005SP003031) |
| 10-20-2005 through 10-27-2005 | NDA | Communications between Sepracor and FDA regarding the process, principal point of contact, timeframe and payment ID number for Sepracor to pay the user fee for NDA 21-912 through the new FDA Web-based system |
| 11-3-2005 | IND | 15-Day IND Safety Report: Follow-Up Report (2005SP003031) |
| 11-7-2005 | NDA | Communication between Sepracor and FDA regarding the status of the tradename submission (serial no. 385) |
| 11-8-2005 | NDA | Payment of NDA 21-912 user fee |
| 11-10-2005 | IND | Protocol Amendment: New Investigators (27) for 091-061 |
| 11-15-2005 | NDA | Confirmation of payment of NDA 21-912 user fee |
| 11-29-2005 | NDA | Communication between Sepracor and FDA regarding an approximate date for submission of the NDA |
| 12-8-2005 (A) | IND | Protocol Amendment: New Investigators (22) for 091-061 |
| **12-8-2005 (B)** | NDA | **Original submission of eNDA for Arformoterol** |
| 12-15-2005 | NDA | Communication between Sepracor and FDA regarding the submission of eNDA and confirmation by FDA that the eNDA had been received on 12/12/05 |
| 12-16-2005 | NDA | Communication from FDA to Sepracor to confirm that the NDA 21-912 had been received on 12/12/2005 |
| 12-20-2005 (A) | NDA | Communication from FDA to Sepracor requesting resubmission of eNDA which was not readable |
| 12-20-2005 (B) | NDA | Communication regarding the unreadable DLT tape that contained the eNDA |
| 12-20-2005 (C) | NDA | Communication from FDA regarding the available options for resubmission of the eNDA |
| 12-20-2005 (D) | NDA | Resubmission of the Arformoterol eNDA - an exact copy of the original submission |
| 12-21-2005 | NDA | Communication between Sepracor and FDA regarding the resubmission of eNDA |
| 12-28-2005 (A) | NDA | Communication from FDA to Sepracor providing a fax copy of the letter from FDA regarding the proposed trade name of EXPEDE |
| 12-28-2005 (B) | NDA | Communication by FDA requesting second resubmission of the eNDA |

| Date | Type | Activity |
|---|---|---|
| 1-3-2006 (A) | NDA | Communication between Sepracor and FDA regarding submission of additional trade names |
| 1-3-2006 (B) | NDA | Communications between Sepracor and FDA regarding the status of eNDA |
| 1-3-2006 (C) | NDA | A copy of the fax sent on 12/28/2005 requesting resubmission of the eNDA |
| 1-3-2006 (D) | NDA | Communication from Sepracor to FDA regarding the status of the re-submission of the eNDA on 12/20/2005 |
| 1-3-2006 (E) | NDA | Communication from Sepracor to FDA regarding the cause of the defect in the tape |
| 1-3-2006 (F) | NDA | Communication from Sepracor to FDA regarding second resubmission of eNDA |
| 1-4-2006 (A) | NDA | Communication from Sepracor to FDA seeking confirmation of FDA's receipt of eNDA |
| 1-4-2006 (B) | NDA | Communication between Sepracor and FDA regarding the status of the eNDA and the receipt/action date of the eNDA |
| 1-4-2006 (C) | NDA | Communication between Sepracor and FDA regarding the status of the DVD copies of eNDA |
| 1-4-2006 (D) | NDA | Request by FDA for third resubmission of eNDA - an exact copy of the original submission |
| 1-5-2006 (A) | NDA | Discussion regarding the situation with the multiple resubmission of the eNDA |
| 1-5-2006 (B) | NDA | Inquiry by Sepracor as to the issues with regard to the multiple resubmission of the eNDA |
| 1-6-2006 (A) | NDA | Communication from Sepracor to FDA regarding the status of the latest eNDA submission |
| 1-6-2006 (B) | NDA | Communication from Sepracor to FDA regarding the status of the latest eNDA submission |
| 1-6-2006 (C) | NDA | Third resubmission of the Arformoterol eNDA - an exact copy of the original submission |
| 1-6-2006 (D) | NDA | Cover letter for the 3rd re-submission of the Arformoterol eNDA |
| 1-6-2006 (E) | NDA | Communication between Sepracor and FDA regarding the status of the eNDA and the NDA acknowledgement letter |
| 1-9-2006 (A) | NDA | Communication between Sepracor and FDA regarding the status of the NDA acknowledgement letter |
| 1-9-2006 (B) | NDA | Communication between Sepracor and FDA regarding the latest submission of eNDA |
| 1-12-2006 | IND | Protocol Amendment: New Investigators (Protocol 091-061) |
| 1-13-2006 | NDA | Continuing to seek the status of the NDA acknowledgement letter with no definite outcome |
| 1-17-2006 | NDA | Continuing to seek the status of the NDA acknowledgement letter with no definite outcome |

| Date | Type | Activity |
|---|---|---|
| 1-18-2006 | NDA | Request by Sepracor for the status of the NDA acknowledgement letter with no definite outcome |
| 1-19-2006 (A) | NDA | Continuing to seek the status of the NDA acknowledgement letter with no definite outcome |
| 1-19-2006 (B) | NDA | Continuing to seek the status of the NDA acknowledgement letter with no definite outcome |
| 1-20-2006 | NDA | Sepracor bringing the discussion to the next level at FDA, inquiring about the status of the NDA acknowledgement letter with no definite outcome |
| 1-21-2006 | NDA | Sepracor bringing the discussion to the next level at FDA, inquiring about the status of the NDA acknowledgement letter with no definite outcome |
| 1-23-2006 | NDA | Continuing to seek the status of the NDA acknowledgement letter with no outcome |
| 1-24-2006 (A) | NDA | Discussions between Sepracor and FDA regarding the problems with the DLT tapes |
| 1-24-2006 (B) | NDA | Sepracor contnuing to seek the status of the NDA acknowledgement letter |
| 1-25-2006 (A) | NDA | Sepracor continuing to seek the status of the acknowledgement letter for the NDA |
| 1-25-2006 (B) | NDA | Communication between Sepracor and FDA regarding the status of the acknowledgement letter for the NDA |
| 1-25-2006 (C) | NDA | Communication from FDA to Sepracor providing a fax copy of the acknowledgement letter for the Arformoterol eNDA |
| 1-25-2006 (D) | NDA | Official acknowledgement of receipt letter from FDA for the Arformoterol eNDA - Date of Receipt is December 12, 2005 |
| 1-26-2006 | NDA | Communication from FDA to Sepracor regarding Sepracor's receipt of the fax and cancellation of the scheduled meeting |
| 1-27-2006 | NDA | Communication between Sepracor and FDA regarding the problems with each of the DLT tapes that were submitted |
| 2-1-2006 (A) | IND | Protocol Amendment: Change in Protocol, New Investigator (091-061) |
| 2-1-2006 (B) | NDA | Communication from Sepracor to FDA regarding secure email set up |
| 2-6-2006 | NDA | Communication from FDA to Sepracor regarding the findings from testing the 3rd DLT tape sent to FDA |
| 2-10-2006 | NDA | Communication between Sepracor and FDA regarding the filing status and the 120 day safety update for Arformoterol |
| 2-16-2006 (A) | IND | Protocol Amendment: Revised Forms FDA 1572 (091-019) |
| 2-16-2006 (B) | NDA | Resubmission of two (2) sections (product.pdf and iss.pdf) of the Arformoterol eNDA that had originally been submitted to FDA on 12/8/2005 and again on 12/20/2005. |

| Date | Type | Activity |
|---|---|---|
| 2-17-2006 | NDA | Communication between Sepracor and FDA between 2/15/2006 and 2/17/2006 regarding: Status of the Tradename submission (Sepracor to FDA); Status of the 74 day letter (FDA to Sepracor); Updated Financial Disclosure Information (Sepracor to FDA); and ECAC comments (FDA to Sepracor) |
| 2-23-2006 (A) | NDA | FDA informed Sepracor that the filing review is complete and the application is sufficient for review |
| 2-23-2006 (B) | NDA | Communication by FDA informing the filing review is complete and the application is sufficient for review with a filing date of 2/10/2006 |
| 2-27-2006 | IND | Submission: 15-Day IND Alert Report: Initial Report –061 (2006SP000798) |
| 3-1-2006 | IND | Submission: 15-Day IND Alert Report: Initial Report –061 (2006SP000853) |
| 3-3-2006 | IND | Submission: 15-Day IND Alert Report: Initial Report –061 (2006SP000799) |
| 3-8-2006 | IND | 7-Day Fax Notification to precede 15-Day Alert Report |
| 3-13-2006 | NDA | Communication between Sepracor and FDA regarding the status of: Pharmacovigilance Proposal, NDA Status, Update on Trade Name Submission, and Pending ECAC Comments |
| 3-14-2006 | IND | Protocol Amendment: Revised Forms FDA 1572 (7 investigators) –091-061 |
| 3-15-2006 | IND | Submission: 15-Day IND Alert Report: 1 initial, 1 follow-up (2006SP001060, 2006SP000853FU1). Note: MFR 2006SP001060 is an initial report that followed a 7-Day Alert Report Fax notification Sepracor sent to FDA on March 8, 2006. |
| 3-21-2006 | IND | Protocol Amendment: Revised Forms FDA 1571 Page 3's for Studies 091-012, 091-013, 091-014, 091-015, 091-016, 091-050 |
| 3-23-2006 | NDA | Communication from FDA to Sepracor providing FDA's questions for nonclinical information in the NDA |
| 3-29-2006 (A) | NDA | Submission by Sepracor of the response to the Division's request for information, as well as corresponding data files and SAS transport files |
| 3-29-2006 (B) | NDA | Communication by Sepracor providing the status of the response to the nonclinical information response |
| 3-30-2006 | IND | Submission: 15-Day IND Alert Report: Initial Report, Follow-Up Report –061 (2006SP000798FU1, 2006SP001343) |
| 3-31-2006 | NDA | Amendment to a Pending Application: Submission of a Proprietary Trade Name - Brovana™ |
| 4-4-2006 | NDA | Communication from FDA to Sepracor regarding: a problem encountered by one of the reviewers in opening the CMC product files; the trade name for Arformoterol and the mid cycle review meeting - May 2, 2006 |
| 4-7-2006 | IND | Submission: 15-Day IND Alert Report: Initial Reports –061 (2006SP001399, 2006SP001493) |
| 4-11-2006 | NDA | General Correspondence: Amendment to a Pending Application: Request for Type C Meeting to discuss proposed pharmacovigilance plan |
| 4-12-2006 | IND | Protocol Amendment: New Investigator, Revised 1572's (091-061) |
| 4-18-2006 | NDA | Amendment: 120-Day Safety Update Report |
| 4-19-2006 (A) | NDA | Communication from Sepracor to FDA informing the submission of the 120-Day Safety Update and inquiring about the request for the Type C Meeting |

| Date | Type | Activity |
|---|---|---|
| 4-19-2006 (B) | NDA | Notification of electronic submission to CDER: Amendment to a pending application - 120-day Safety Update (also to notify the Field Office of the submission of the original NDA) |
| 4-20-2006 | IND | Submission: 15-Day IND Alert Report: Follow-Up Report –061 (2006SP001343FU1) |
| 4-24-2006 | NDA | Communication between Sepracor and FDA regarding confirmation of grant of Type C Meeting request |
| 4-26-2006 | NDA | Communication between Sepracor and FDA regarding the Rat carcinogenicity data sets in the NDA |
| 4-27-2006 | NDA | Amendment: (A2) Replacement of Nonclinical Toxicology Datasets from study 090-828A2 |
| 4-28-2006 | IND | Submission: 15-Day IND Alert Report: Initial Report –061 (2006SP001746) |
| 5-3-2006 | NDA | Communication from FDA to Sepracor informing that no additional issues identified during FDA mid cycle review meeting |
| 5-15-2006 (A) | NDA | General Correspondence: Briefing Document for Type C Meeting |
| 5-15-2006 (B) | NDA | Communication from Sepracor to FDA regarding the status of the briefing document, trade name submission and the scheduling of GCP audits |
| 5-17-2006 | IND | Submission: IND Annual Report (April 1, 2005 – March 15, 2006) |
| 5-18-2006 | IND | Protocol Amendment: New Investigator, Revised Forms FDA 1572 (091-061) |
| 5-19-2006 | IND | Submission: 15-Day IND Alert Report: Initial Report –061 (2006SP002030) |
| 5-25-2006 | IND | Submission: 15-Day IND Alert Report: Initial Report –061 (2006SP002061) Follow-Up Report (2006SP001399FU1) |
| 6-6-2006 | IND | Submission: 15-Day IND Alert Report: Initial Report –061 Initial Report (2006SP002192) |
| 6-7-2006 (A) | IND | Protocol Amendment: Change in Protocol, New Investigator, Revised Forms FDA 1572 (091-061) |
| 6-7-2006 (B) | NDA | Communication from FDA to Sepracor providing review questions for CMC on the NDA regarding the Sterility Assurance Validation Report; Acceptance criteria for the environmental monitoring program; bacteriostasis/ fungistasis data used for validation of the use of the sterility test with the subject drug product |
| 6-13-2006 (A) | IND | Submission: 15-Day IND Alert Report: Initial Report –061 Initial Report (2006SP002268), Follow-Up Report (2006SP001399FU2) |
| 6-13-2006 (B) | NDA | Request for samples by FDA |
| 6-15-2006 | NDA | Email from Sepracor to FDA providing update on the two outstanding CMC requests |
| 6-16-2006 | NDA | FDA Response to questions in the May 15, 2006 Meeting Package regarding Pharmacovigilance Plan |
| 6-19-2006 (A) | NDA | E-mails between Sepracor and FDA regarding FDA's request for samples |
| 6-19-2006 (B) | NDA | Discussion of FDA's fax responses to the proposed Pharmacovigilance Plan |
| 6-23-2006 (A) | IND | Submission: 15-Day IND Alert Report: Initial Report –061 Initial Report (2006SP002375), Follow-Up Report (2006SP001493FU1) |

| Date | Type | Activity |
|---|---|---|
| 6-23-2006 (B) | NDA | Amendment: Response to FDA Request for Information to Evaluate the Sterility Assurance of the Drug Product |
| 6-23-2006 (C) | NDA | Communication between Sepracor and FDA regarding the packaging of commercial vials |
| 6-26-2006 | NDA | Notification of electronic submission to CDER: Amendment to a Pending Application - Response to FDA Request for Information to Evaluate the Sterility Assurance of the Drug Product |
| 6-27-2006 (A) | NDA | Review letter from FDA requesting additional information for the CMC reviewers on the NDA |
| 6-27-2006 (B) | NDA | Fax of the letter from FDA requesting additional information for CMC reviewers on the NDA |
| 6-27-2006 (C) | NDA | Arformoterol Tartrate Inhalation Solution Pharmacovigilance meeting Executive Summary, June 27, 2006 |
| 6-28-2006 | IND | Submission: 15-Day IND Alert Report: Initial Report –061 Initial Report (2006SP002534), Follow-Up Report (2006SP002192FU1, 2268FU1) |
| 6-29-2006 | NDA | Communication from FDA to Sepracor regarding the status of the alternate trade name submission |
| 7-10-2006 | NDA | General Correspondence: FDA Request for Samples of Arformoterol |
| 7-11-2006 (A) | NDA | Communication between Sepracor and FDA regarding the status of several submissions surrounding the Arformoterol NDA |
| 7-11-2006 (B) | NDA | Fax copy of the official FDA meeting minutes from the meeting between Sepracor and FDA on June 27, 2006 |
| 7-12-2006 (A) | IND | Submission: 15-Day IND Alert Report: Follow-Up Report –061 (2006SP002534FU1) |
| 7-12-2006 (B) | NDA | Amendment: Response to Chemistry Discipline Review Letter |
| 7-12-2006 (C) | NDA | Notification of electronic submission to CDER: Amendment: Response to Chemistry Discipline Review Letter |
| 7-13-2006 (A) | NDA | General Correspondence: Type C Meeting Follow Up (Pharmacovigilance Plan). |
| 7-13-2006 (B) | NDA | Communication from Sepracor to FDA providing the cover letter from the arformoterol samples submission dated 7/10/2006 |
| 7-13-2006 (C) | NDA | Communication from Sepracor to FDA providing the follow up letter to the Pharmacovilgilance meeting held on June 27, 2006 which was submitted to the NDA on 7/13/2006 |
| 7-19-2006 (A) | IND | Protocol Amendment: New Investigator, Revised Forms FDA 1572 (091-061) |
| 7-19-2006 (B) | NDA | Communication from Sepracor to FDA regarding the status of the Trade name submissions for Arformoterol |
| 7-21-2006 | NDA | Amendment to a Pending Application: Submission of a Proprietary Trade Name - Arformex™ |
| 7-25-2006 | NDA | Communication between Sepracor and FDA regarding the information request made by FDA regarding the pooled pivotal clinical trails 091-050 an 091-051 |

| Date | Type | Activity |
|---|---|---|
| 7-27-2006 | NDA | Communication from FDA to Sepracor regarding the trade names and the submission of subsequent information on the asthma outline/synopsis discussed in the pharmacovigilance meeting 6/27/2006 |
| 8-3-2006 (A) | NDA | General Correspondence: Response to Clinical Request for Information |
| 8-3-2006 (B) | NDA | Communication from Sepracor to FDA regarding the incoming General Correspondence: Response to Clinical Request for Information that was submitted to FDA on August 3, 2006 |
| 8-4-2006 | IND | Submission: 15-Day IND Alert Report: Initial Report –061 (2006SP002771) |
| 8-7-2006 | NDA | Communication from FDA to Sepracor regarding the engraving on the vials |
| 8-9-2006 (A) | IND | Submission: 15-Day IND Alert Report: Initial Report –061 (2006SP002838) Follow-Up Report (2006SP002192FU2) |
| 8-9-2006 (B) | NDA | Communication from FDA to Sepracor regarding the annotated label in the NDA |
| 8-16-2006 | IND | Submission: 15-Day IND Alert Report: Initial Report –061 Follow-Up Reports (2006SP001060FU1, 2375FU1) |
| 8-21-2006 (A) | IND | Submission: 15-Day IND Alert Report: Initial Report –061 Initial Report (2006SP002955), Follow-Up Report (2006SP002771FU1) |
| 8-21-2006 (B) | IND | Protocol Amendment: New Investigators, Revised Forms FDA 1572 (091-061) |
| 8-22-2006 | NDA | FDA's response to an earlier e-mail by Sepracor regarding several issues in connection with the NDA (labeling/trade name/any outstanding issues) |
| 8-28-2006 | NDA | Communication from FDA to Sepracor providing CMC questions regarding the Response to the Chemistry Discipline Review Letter submission (7-12-2006) |
| 8-29-2006 | NDA | General Correspondence: Proposed Pediatric Asthma Plan |
| 8-30-2006 | IND | Submission: 15-Day IND Alert Report: Initial Report –061 Initial Report (2006SP003066), Follow-Up Reports (2006SP002268FU2, 2838FU1) |
| 9-5-2006 | IND | Submission: 15-Day IND Alert Report: Follow-Up Report –061 (2006SP001746FU1) |
| 9-7-2006 | IND | Submission: 15-Day IND Alert Report: Follow-Up Report –061 (2006SP002955FU1) |
| 9-8-2006 | NDA | Communication from Sepracor to FDA providing update on FDA's question regarding the actual embossing plan for Arformoterol vials |
| 9-11-2006 (A) | NDA | Communication between Sepracor and FDA regarding regarding the timing of the response to the CMC information request will be sent in |
| 9-11-2006 (B) | NDA | Communication from FDA to Sepracor regarding rescheduling of the date of the Labeling Teleconference |
| 9-12-2006 (A) | IND | Submission: 15-Day IND Alert Report: Initial Report –061 Initial Report (2006SP003159, 3160), Follow-Up Report (2006SP002771FU2) |
| 9-12-2006 (B) | NDA | FDA communication to Sepracor regarding proposed trade names |
| 9-12-2006 (C) | NDA | Amendment to a Pending Application: Response to Chemistry Request for Information Letter dated 28 August 2006 |

| Date | Type | Activity |
|---|---|---|
| 9-12-2006 (D) | NDA | Notification of electronic submission to CDER: Response to Chemistry Request for Information Letter dated 28 August 2006 |
| 9-12-2006 (E) | NDA | Communication between Sepracor and FDA regarding CMC Information Request response documents |
| 9-14-2006 | NDA | Communication from FDA to Sepracor requesting results from *in vitro* characterization studies |
| 9-15-2006 | NDA | Communication between Sepracor and FDA regarding the timing of the CMC response (*in vitro* characterization studies) |
| 9-19-2006 (A) | NDA | Communication from FDA to Sepracor regarding FDA comments on draft labeling |
| 9-19-2006 (B) | NDA | Communication from Sepracor to FDA acknowledging receipt of the e-mail and fax concerning draft labeling comments |
| 9-19-2006 (C) | NDA | Communication from Sepracor to FDA with questions on the comments made by FDA on the labeling |
| 9-20-2006 (A) | NDA | Communication between Sepracor and FDA regarding the CMC reviewer's questions |
| 9-20-2006 (B) | NDA | General Correspondence: Response to FDA Request for CMC Information |
| 9-21-2006 (A) | NDA | Response by FDA to questions from Sepracor regarding FDA's comments on draft labeling for Arformoterol |
| 9-21-2006 (B) | NDA | Communication between Sepracor and FDA regarding the issues concerning trade name |
| 9-22-2006 (A) | NDA | Communication from FDA to Sepracor regarding the final decision concerning the trade name situation |
| 9-22-2006 (B) | NDA | Request by FDA for the revised PI |
| 9-22-2006 (C) | NDA | Communication from Sepracor to FDA providing the medication guide and responses to the fax |
| 9-22-2006 (D) | NDA | Communication from Sepracor to FDA providing the vial and foil for packaging |
| 9-25-2006 | NDA | Communication from Sepracor to FDA providing the revised carton file |
| 9-26-2006 | NDA | Sepracor version of the meeting minutes from the teleconference held between Sepracor and FDA on label negotiations. Communication between Sepracor and FDA regarding labeling issues and postmarketing issues |
| 9-27-2006 (A) | IND | Submission: 15-Day IND Alert Report: Initial Report –061 (2006SP003265) |
| 9-27-2006 (B) | NDA | Amendment to a Pending Application: Response to FDA Correspondence Regarding Proposed Labeling |
| 9-28-2006 (A) | NDA | Response from FDA to Sepracor's submission of 9/27/2006 concerning labeling |
| 9-28-2006 (B) | NDA | Communication from Sepracor to FDA regarding post marketing commitments from FDA |

| Date | Type | Activity |
|---|---|---|
| 10-2-2006 (A) | NDA | Communication from FDA to Sepracor regarding the Post marketing study requirements |
| 10-2-2006 (B) | NDA | Request by FDA for official submission to the NDA of the proposed labeling from 10/2/2006 |
| 10-3-2006 (A) | IND | Submission: 15-Day IND Alert Report: Follow-Up Report –061 (2006SP001746FU2) |
| 10-3-2006 (B) | NDA | Communication from FDA to Sepracor regarding FDA responses to the labeling submitted on October 2, 2006 |
| 10-3-2006 (C) | NDA | Fax from FDA with responses to the labeling submitted by Sepracor on October 2, 2006 |
| 10-3-2006 (D) | NDA | Communication from Sepracor to FDA regarding the integration of the feedback from FDA into the draft PI |
| 10-4-2006 (A) | NDA | General Correspondence: Proposal for Revised Draft Package Insert |
| 10-4-2006 (B) | NDA | Communication from Sepracor to FDA regarding the revised labeling (package insert, medication guide, carton 30/60 count and pouch) |
| 10-4-2006 (C) | NDA | Communication from Sepracor to FDA forwarding the 10/4/2006 version of the package insert-both clean and track changes along with the post marketing commitment letter |
| 10-3-2006 (D) | NDA | Formal Submission of General Correspondence Letter previously e-mailed to FDA on 10/4/2006. |
| 10-4-2006 (E) | NDA | Communication from FDA to Sepracor providing changes to the package insert |
| 10-5-2006 (A) | NDA | Communication from Sepracor to FDA providing the 10/5/2006 version of the package insert-both clean and track changes |
| 10-5-2006 (B) | NDA | Amendment to a Pending Application: Final Labeling |
| 10-5-2006 (C) | NDA | Communication from Sepracor to FDA providing the revised PI with the changes requested by FDA |
| 10-5-2006 (D) | NDA | The final package insert (clean and tracked changes versions) |
| **10-6-2006** | **NDA** | **FDA official letter to approve Brovana NDA and also the final printed labeling** |